SUBSTITUTED-QUINOXALINE-TYPE BRIDGED-PIPERIDINE COMPOUNDS AND THE USES THEREOF

1. FIELD OF THE INVENTION

The invention relates to Substituted-Quinoxaline-Type Bridged-Piperidine Compounds, compositions comprising an effective amount of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound and methods to treat or prevent a condition, such as pain, comprising administering to an animal in need thereof an effective amount of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound.

2. BACKGROUND OF THE INVENTION

Chronic pain is a major contributor to disability and is the cause of much suffering. The successful treatment of severe and chronic pain is a primary goal of the physician, with opioid analgesics being preferred drugs for doing so.

Until recently, there was evidence of three major classes of opioid receptors in the central nervous system (CNS), with each class having subtype receptors. These receptor classes are known as μ, κ and δ. As opiates have a high affinity for these receptors while not being endogenous to the body, research followed in order to identify and isolate the endogenous ligands to these receptors. These ligands were identified as enkephalins, endorphins and dynorphins.

Recent experimentation has led to the identification of a cDNA encoding an opioid receptor-like (ORL-1) receptor with a high degree of homology to the known receptor classes. The ORL-1 receptor was classified as an opioid receptor based only on structural grounds, as the receptor did not exhibit pharmacological homology. It was initially demonstrated that non-selective ligands having a high affinity for μ, κ and δ receptors had low affinity for the ORL-1 receptor. This characteristic, along with the fact that an endogenous ligand had not yet been discovered, led to the term "orphan receptor".

Subsequent research led to the isolation and structure of the endogenous ligand of the ORL-1 receptor (*i.e.*, nociceptin). This ligand is a seventeen amino acid peptide structurally similar to members of the opioid peptide family.

The discovery of the ORL-1 receptor presents an opportunity in drug discovery for novel compounds that can be administered for pain management or other syndromes modulated by this receptor.

International PCT Publication No. WO 99/46260 A1 describes quinoxalinone derivatives as inhibitors of protein kinase C.

International PCT Publication No. WO 99/50254 A1 describes quinoxalinone derivatives as serine protease inhibitors.

International PCT Publication No. WO 01/90102 A2 describes 6-heterocyclyl-3-oxo-3,4-dihydro-quinoxalines for use as herbicides.

International PCT Publication No. WO 2003/062234 A1 describes quinoxaline derivatives for use in remedying diseases in which poly(ADP-ribose) polymerase (PARP) participates.

U.S. published patent application No. US 2005/0256000 by Schaper *et al.* describes quinoxaline-2-one derivatives for use as safeners for plants.

International PCT Publication No. WO 2005/028451 A1 describes tetrahydroquinoxaline derivatives for use as M2 acetylcholine receptor agonists.

International PCT Publication No. WO 2009/027820 A2 describes substituted-quinoxaline-type piperidine compounds for use in treating or preventing, *e.g.*, pain.

Citation of any reference in Section 2 of this application is not to be construed as an admission that such reference is prior art to the present application.

3. SUMMARY OF THE INVENTION

It is an object of the invention to provide new compounds that exhibit affinity for the ORL-1 receptor.

In certain embodiments of the invention, such new compounds exhibit agonist activity at the ORL-1 receptor.

In certain embodiments of the invention, such new compounds exhibit partial agonist activity at the ORL-1 receptor.

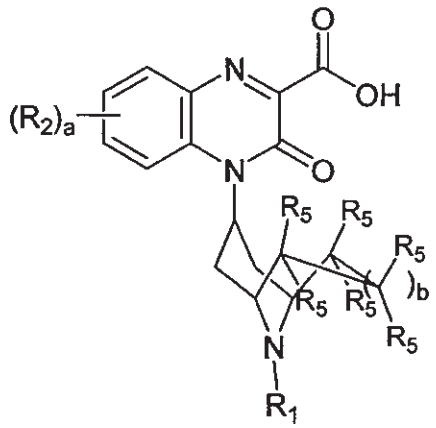
In certain other embodiments of the invention, such new compounds exhibit antagonist activity at the ORL-1 receptor.

In certain embodiments of the invention, such new compounds exhibit affinity for the ORL-1 receptor, and also for one or more of the μ, κ or δ receptors. In a particular embodiment, a new compound of the invention exhibits affinity for both the ORL-1 receptor and the μ receptor. In another embodiment, a new compound of the invention acts as an ORL-1 receptor agonist and as a μ receptor agonist. In another embodiment, a new compound of the invention acts as an ORL-1 receptor partial agonist and as a μ receptor agonist. In another embodiment, a new compound of the invention acts as an ORL-1 receptor partial agonist and as a μ receptor antagonist. In another embodiment, a new compound of the invention acts as an ORL-1 receptor antagonist and as a μ receptor agonist.

Certain new compounds of the invention can be used to treat an animal suffering from chronic or acute pain.

It is a further object of the invention to provide methods of treating chronic or acute pain in an animal by administering one or more Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention to an animal in need of such treatment. In certain embodiments, such new Substituted-Quinoxaline-Type Bridged-Piperidine Compounds effectively treat chronic or acute pain in the animal, while producing fewer or reduced side effects compared to previously available compounds. For example, Substituted Quinoxaline-Type Bridged-Piperidine Compounds **358**, **361**, and **362** have surprisingly and desirably reduced abnormal behavioral side effects, such as reduced sedation, hyperactivity and/or hypoactivity. Additionally and surprisingly, Substituted Quinoxaline-Type Bridged-Piperidine Compound **362** has reduced cardiovascular side effects. These side effects were determined using known methods: an *in vitro* hERG (human ether a-go-go gene) assay as disclosed in Z. Zhou et al., "Properties of HERG Channels Stably Expressed in HEK 293 Cells Studied at Physiological Temperature," *Biophysical J.* 74:230-241 (1998); and APD (action potential duration) in guinea pig purkinje fibers as disclosed in J.A. Hey, "The Guinea Pig Model for Assessing Cardiotoxic Proclivities of Second Generation Antihistamines," *Arzneimittelforschung* 46(8):834-837 (1996).

The invention encompasses compounds of Formula (I):



(I)

or a pharmaceutically acceptable derivative thereof wherein:

each R_2 is independently selected from -halo;

a is an integer selected from 0, 1 or 2;

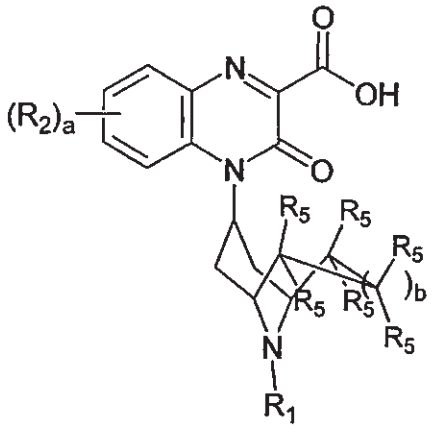
b is an integer selected from 0 or 1;

each R_5 is independently selected from -H, -OH, -(C_1-C_3)alkyl, -C(halo)$_3$, or -halo;

R_1 is -(C_9-C_{14})cycloalkyl or -(C_9-C_{14})bicycloalkyl; and

each halo is independently selected from -F, -Cl, -Br, or -I.

The invention also encompasses compounds of Formula (I'):



(I')

or a pharmaceutically acceptable derivative thereof wherein:

each R_2 is independently selected from -halo;

a is an integer selected from 0, 1 or 2;

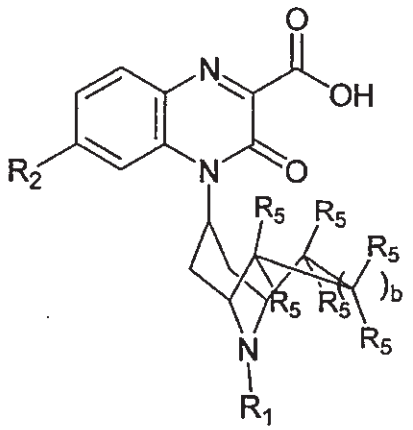
b is an integer selected from 0 or 1;

each R_5 is independently selected from -H, -OH, -(C_1-C_3)alkyl, -C(halo)$_3$, or -halo;

R_1 is -(C_9-C_{14})cycloalkyl or -(C_9-C_{14})bicycloalkyl, each of which is substituted with 1, 2 or 3 independently selected R_3 groups;

each R_3 is independently selected from -(C_1-C_4)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, or -(C_3-C_6)cycloalkyl.

The invention also encompasses compounds of Formula (II):



(II)

or a pharmaceutically acceptable derivative thereof where R_1, R_2, R_5, and b are defined above for the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of Formulae (I) or (I').

A compound of Formula (I), Formula (I') or Formula (II) or a pharmaceutically acceptable derivative thereof (a "Substituted-Quinoxaline-Type Bridged-Piperidine Compound") is useful, *e.g.*, as an analgesic, anti-inflammatory, diuretic, anesthetic agent, neuroprotective agent, anti-hypertensive, an anxiolytic agent, an agent for appetite control, hearing regulator, anti-tussive, anti-asthmatic, modulator of locomotor activity, modulator of learning and memory, regulator of neurotransmitter release, regulator of hormone release, kidney function modulator, anti-depressant, agent to treat memory loss due to Alzheimer's disease and/or other dementias, anti-epileptic, anti-convulsant, agent to treat withdrawal from alcohol, agent to treat withdrawal from drug(s) of addiction, agent to control water balance, agent to control sodium excretion, and/or agent to control arterial blood pressure disorder(s).

A Substituted-Quinoxaline-Type Bridged-Piperidine Compound is useful for treating and/or preventing pain, anxiety, cough, diarrhea, high blood pressure, epilepsy, anorexia/cachexia, urinary incontinence, drug abuse, a memory disorder, obesity, constipation, depression, dementia, or Parkinsonism (each being a "Condition") in an animal.

The invention also relates to compositions comprising an effective amount of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound and a pharmaceutically acceptable carrier or excipient. The compositions are useful for treating or preventing a Condition in an animal.

The invention further relates to methods for treating a Condition, comprising administering to an animal in need thereof an effective amount of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound.

The invention further relates to methods for preventing a Condition, comprising administering to an animal in need thereof an effective amount of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound.

The invention further relates to the use of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound, *e.g.*, of Formulas (I), (I') and/or (II), for the manufacture of a medicament useful for treating a Condition.

The invention further relates to the use of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound, *e.g.*, of Formulas (I), (I') and/or (II), for the manufacture of a medicament useful for preventing a Condition.

The invention still further relates to methods for inhibiting ORL-1 receptor function in a cell, comprising contacting a cell capable of expressing the ORL-1 receptor with an ORL-1 receptor function inhibiting amount of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound.

The invention still further relates to methods for activating ORL-1 receptor function in a cell, comprising contacting a cell capable of expressing the ORL-1 receptor with an ORL-1 receptor function activating amount of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound.

The invention still further relates to methods for preparing Substituted-Quinoxaline-Type Bridged-Piperidine Compounds and/or pharmaceutically acceptable derivatives thereof. Such methods are illustrated in the synthetic Schemes and Examples herein.

The invention still further relates to methods for preparing a composition, comprising the step of admixing a Substituted-Quinoxaline-Type Bridged-Piperidine Compound and a pharmaceutically acceptable carrier or excipient.

The invention still further relates to a kit comprising a container containing an effective amount of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound.

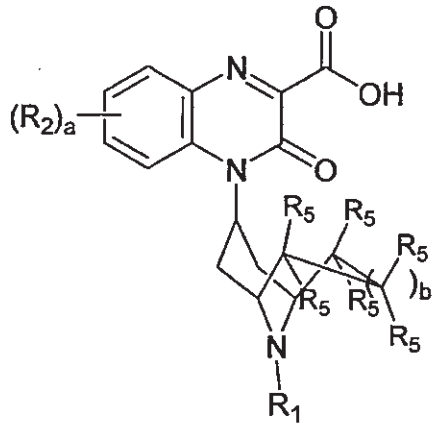
The invention also provides novel intermediates for use in making the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds.

The invention can be understood more fully by reference to the following detailed description and illustrative examples, which are intended to exemplify non-limiting embodiments of the invention. Other objects and advantages of the invention will become apparent from the following detailed description thereof.

4. DETAILED DESCRIPTION OF THE INVENTION

4.1 Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of Formula (I)

As stated above, the invention encompasses Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of Formula (I):



(I)

or a pharmaceutically acceptable derivative thereof where R_1, R_2, R_5, a, and b are defined above for the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of Formula (I).

In one embodiment, R_1 is -(C_9-C_{14})cycloalkyl.

In another embodiment, R_1 is -(C_{11}-C_{14})cycloalkyl.

In another embodiment, R_1 is -(C_{11})cycloalkyl.

In another embodiment, R_1 is -(C_{12})cycloalkyl.

In another embodiment, R_1 is -(C_{13})cycloalkyl.

In another embodiment, R_1 is -(C_{14})cycloalkyl.

In another embodiment, R_1 is -(C_{10}-C_{14})bicycloalkyl.

In another embodiment, R_1 is -indanyl, -1,2,3,4-tetrahydronaphthalenyl, -5,6,7,8-tetrahydronaphthalenyl, -perhydronaphthalenyl, bicyclo[3.3.1]nonyl, bicyclo[4.2.1]nonyl, bicyclo[3.3.2]decyl, bicyclo[4.2.2]decyl, bicyclo[4.3.1]decyl, bicyclo[3.3.3]undecyl, bicyclo[4.3.2]undecyl, or bicyclo[4.3.3]dodecyl.

In another embodiment, R_1 is bicyclo[3.3.1]nonyl.

In another embodiment, R_1 is not 1-bicyclo[3.3.1]nonyl, when R_1 is attached to 9-azabicyclo[3.3.1]nonan-1-yl.

In another embodiment, R_1 is not 9-bicyclo[3.3.1]nonyl, when R_1 is attached to 9-azabicyclo[3.3.1]nonan-1-yl.

In another embodiment, R_1 is not 9-bicyclo[3.3.1]nonyl, when R_1 is attached to 8-azabicyclo[3.2.1]octan-1-yl.

In another embodiment, R_1 is 2-bicyclo[3.3.1]nonyl, or 3-bicyclo[3.3.1]nonyl.

In another embodiment, R_1 is not 9-bicyclo[3.3.1]nonyl.

In another embodiment, R_1 is not 1-bicyclo[3.3.1]nonyl.

In another embodiment, R_1 is -(C_{11}-C_{14})cycloalkyl or -(C_{10}-C_{14})bicycloalkyl.

In another embodiment, R_1 is 1-bicyclo[3.3.1]nonyl, 2-bicyclo[3.3.1]nonyl, 3-bicyclo[3.3.1]nonyl, or -(C_{10}-C_{14})bicycloalkyl.

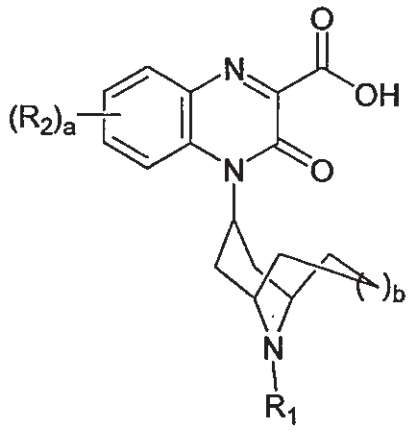
In another embodiment, R_1 is 1-bicyclo[3.3.1]nonyl, 2-bicyclo[3.3.1]nonyl, 3-bicyclo[3.3.1]nonyl, or -(C_{11}-C_{14})cycloalkyl.

In another embodiment, R_1 is -(C_{11}-C_{14})cycloalkyl, 1-bicyclo[3.3.1]nonyl, 2-bicyclo[3.3.1]nonyl, 3-bicyclo[3.3.1]nonyl, or -(C_{10}-C_{14})bicycloalkyl.

In another embodiment, each R_5 is independently selected from -H, -(C_1-C_3)alkyl, -C(halo)$_3$, or -halo.

In another embodiment, each R_5 is independently selected from -H, -CH_3, -CF_3, or -F.

In another embodiment, each R_5 is -H, *i.e.*, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound is a compound of Formula (IA):



(IA)

or a pharmaceutically acceptable derivative thereof where R_1, R_2, a, and b are defined above for the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of Formula (I).

In another embodiment, a is an integer selected from 0 or 1.

In another embodiment, R_2 is -halo.

In another embodiment, R_2 is -F.

In another embodiment, a is 0.

In another embodiment, the 3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid portion of the Substituted-Quinoxaline-Type Bridged-Piperidine Compound is in the *endo-* or *exo-* conformation with respect to the bridge of the bridged piperidine.

In another embodiment, the 3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid portion of the Substituted-Quinoxaline-Type Bridged-Piperidine Compound is in the *endo-* conformation with respect to the bridge of the bridged piperidine.

In another embodiment, the 3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid portion of the Substituted-Quinoxaline-Type Bridged-Piperidine Compound is in the *exo-* conformation with respect to the bridge of the bridged piperidine.

In another embodiment, R_1 is -(C_9-C_{12})cycloalkyl or -(C_9-C_{12})bicycloalkyl.

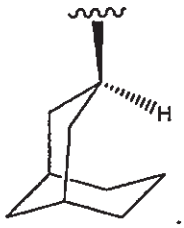
In another embodiment, R_1 is -(C_9-C_{12})bicycloalkyl.

In another embodiment, R_1 is in the *endo-* or *exo-* conformation with respect to the bridge of the bridged piperidine.

In another embodiment, R_1 is in the *endo-* conformation with respect to the bridge of the bridged piperidine.

In another embodiment, R_1 is in the *exo-* conformation with respect to the bridge of the bridged piperidine.

In another embodiment, R_1 is:



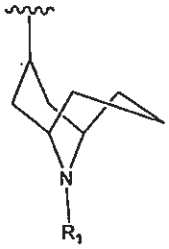
In another embodiment, R_1 is -(C_9-C_{12})cycloalkyl.

In another embodiment, R_1 is -cycloundecyl.

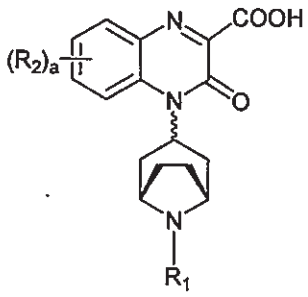
In another embodiment, b is 0, *e.g.*, for a Substituted-Quinoxaline-Type Bridged-Piperidine Compound where each R_5 is -H, the bridged piperidine is:



In another embodiment, b is 1, *e.g.*, for a Substituted-Quinoxaline-Type Bridged-Piperidine Compound where each R_5 is -H, the bridged piperidine is:



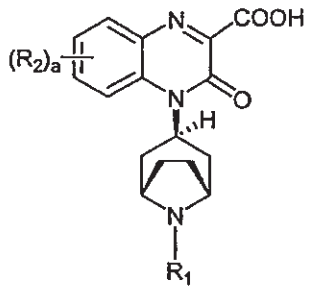
In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (IA) is a Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (IB):



(IB)

wherein R_1, R_2, and a are as defined above for the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of Formula (I).

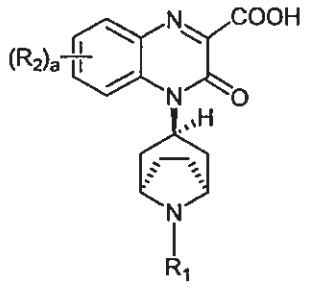
In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (IA) is a Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (IB1):



(IB1)

i.e., a Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (IB) wherein the 6-membered, nitrogen-containing ring that is fused to the benzo is in the *endo*- conformation with respect to the (-CH_2-CH_2-) bridge of the bridged piperidine.

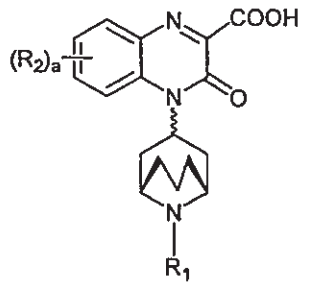
In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (IA) is a Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (IB2):



(IB2)

i.e., a Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (IB) wherein the 6-membered, nitrogen-containing ring that is fused to the benzo is in the *exo*- conformation with respect to the (-CH_2-CH_2-) bridge of the bridged piperidine.

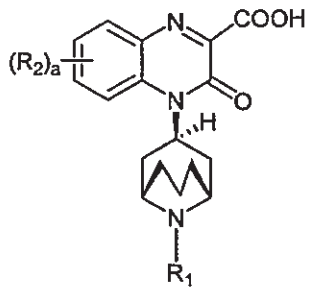
In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (IA) is a Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (IC):



(IC)

wherein R_1, R_2, and a are as defined above for the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of Formula (I).

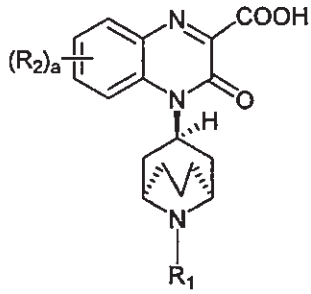
In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (IA) is a Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (IC1):



(IC1)

i.e., a Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (IC) wherein the 6-membered, nitrogen-containing ring that is fused to the benzo is in the *endo*- conformation with respect to the (-CH_2-CH_2-CH_2-) bridge of the bridged piperidine.

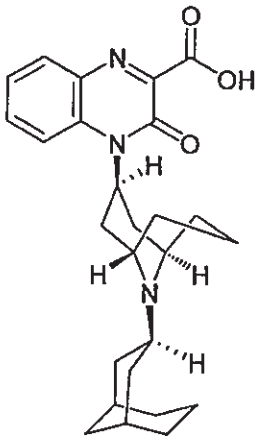
In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (IA) is a Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (IC2):



(IC2)

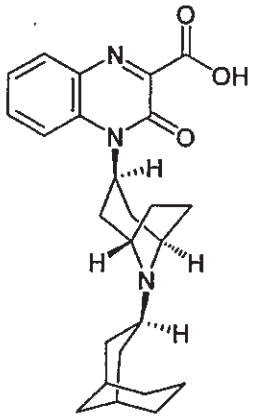
i.e., a Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (IC) wherein the 6-membered, nitrogen-containing ring that is fused to the benzo is in the *exo*- conformation with respect to the (-CH_2-CH_2-CH_2-) bridge of the bridged piperidine.

In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound is:



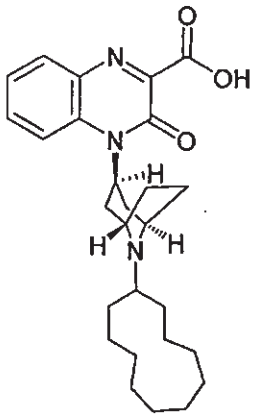
or a pharmaceutically acceptable derivative thereof.

In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound is:



or a pharmaceutically acceptable derivative thereof.

In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound is:



or a pharmaceutically acceptable derivative thereof.

In another embodiment, the pharmaceutically acceptable derivative is a hydrate.

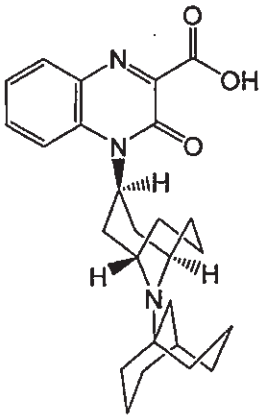
In another embodiment, the pharmaceutically acceptable derivative is a pharmaceutically acceptable salt.

In another embodiment, the pharmaceutically acceptable salt is a *p*-toluenesulfonic acid salt, a sulfate salt, a phosphoric acid salt, or a hydrochloride salt.

In another embodiment, the pharmaceutically acceptable salt is a *p*-toluenesulfonic acid salt, a sulfate salt, or a phosphoric acid salt.

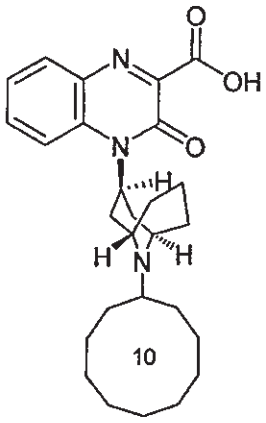
In another embodiment, the pharmaceutically acceptable salt is a *p*-toluenesulfonic acid salt.

In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound is not:



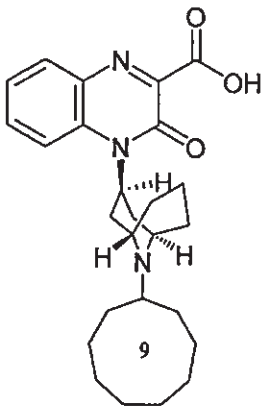
or a pharmaceutically acceptable derivative thereof.

In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound is not:



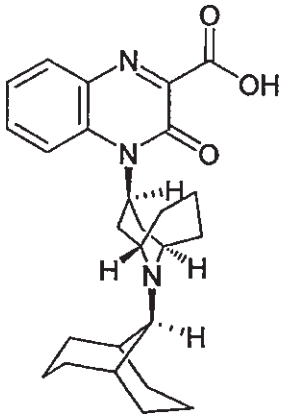
or a pharmaceutically acceptable derivative thereof.

In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound is not:



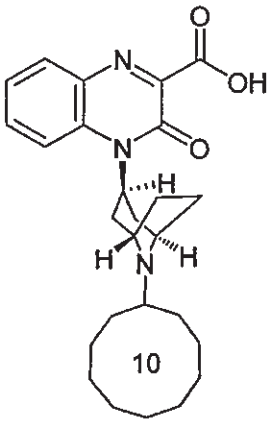
or a pharmaceutically acceptable derivative thereof.

In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound is not:



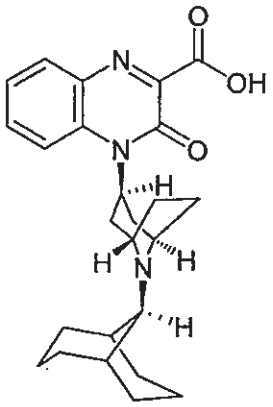
or a pharmaceutically acceptable derivative thereof.

In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound is not:



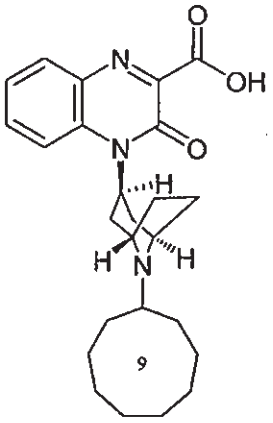
or a pharmaceutically acceptable derivative thereof.

In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound is not:



or a pharmaceutically acceptable derivative thereof.

In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound is not:



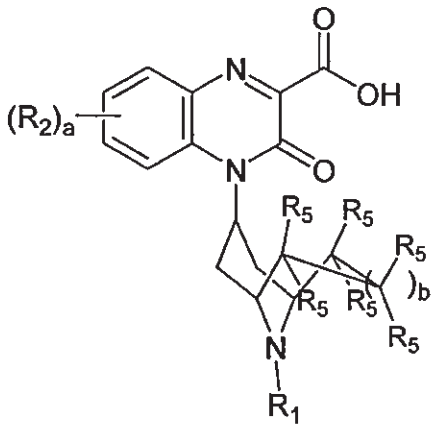
or a pharmaceutically acceptable derivative thereof.

In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound is not 4-(9-(bicyclo[3.3.1]nonan-1-yl)-9-azabicyclo[3.3.1]nonan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid or 4-(9-cyclodecyl-9-azabicyclo[3.3.1]nonan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid or 4-(9-cyclononyl-9-azabicyclo[3.3.1]nonan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid or 4-(9-(bicyclo[3.3.1]nonan-9-yl)-9-azabicyclo[3.3.1]nonan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid or 4-(8-cyclodecyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid or 4-(8-(bicyclo[3.3.1]nonan-9-yl)-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid or 4-(8-cyclononyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid.

In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound is not 4-((*endo*)-9-(bicyclo[3.3.1]nonan-1-yl)-9-azabicyclo[3.3.1]nonan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid or 4-((*endo*)-9-cyclodecyl-9-azabicyclo[3.3.1]nonan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid or 4-((*endo*)-9-cyclononyl-9-azabicyclo[3.3.1]nonan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid or 4-((*endo*)-9-((*exo*)-bicyclo[3.3.1]nonan-9-yl)-9-azabicyclo[3.3.1]nonan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid or 4-((*endo*)-8-cyclodecyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid or 4-((*endo*)-8-((*exo*)-bicyclo[3.3.1]nonan-9-yl)-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid or 4-((*endo*)-8-cyclononyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid.

4.2 Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of Formula (I')

As stated above, the invention encompasses Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of Formula (I'):



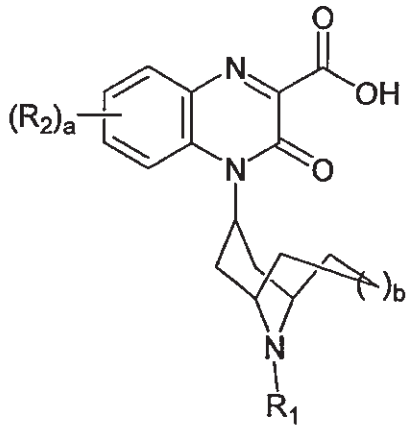
(I')

or a pharmaceutically acceptable derivative thereof where R_1, R_2, R_5, a, and b are defined above for the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of Formula (I').

In one embodiment, each R_5 is independently selected from -H, -(C_1-C_3)alkyl, -C(halo)$_3$, or -halo.

In another embodiment, each R_5 is independently selected from -H, -CH_3, -CF_3, or -F.

In another embodiment, each R_5 is -H, *i.e.*, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound is a compound of Formula (I'A):



(I'A)

or a pharmaceutically acceptable derivative thereof where R_1, R_2, a, and b are defined above for the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of Formula (I').

In another embodiment, a is an integer selected from 0 or 1.

In another embodiment, R_2 is -halo.

In another embodiment, R_2 is -F.

In another embodiment, a is 0.

In another embodiment, the 3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid portion of the Substituted-Quinoxaline-Type Bridged-Piperidine Compound is in the *endo*- or *exo*- conformation with respect to the bridge of the bridged piperidine.

In another embodiment, the 3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid portion of the Substituted-Quinoxaline-Type Bridged-Piperidine Compound is in the *endo*- conformation with respect to the bridge of the bridged piperidine.

In another embodiment, the 3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid portion of the Substituted-Quinoxaline-Type Bridged-Piperidine Compound is in the *exo*- conformation with respect to the bridge of the bridged piperidine.

In another embodiment, R_1 is -(C_9-C_{12})cycloalkyl or -(C_9-C_{12})bicycloalkyl.

In another embodiment, R_1 is -(C_9-C_{12})bicycloalkyl.

In another embodiment, R_1 is bicyclo[3.3.1]nonyl.

In another embodiment, R_1 is 1-bicyclo[3.3.1]nonyl, 2-bicyclo[3.3.1]nonyl, or 3-bicyclo[3.3.1]nonyl.

In another embodiment, R_1 is in the *endo*- or *exo*- conformation with respect to the bridge of the bridged piperidine.

In another embodiment, R_1 is in the *endo*- conformation with respect to the bridge of the bridged piperidine.

In another embodiment, R_1 is in the *exo*- conformation with respect to the bridge of the bridged piperidine.

In another embodiment, there are three independently-selected R_3 groups.

In another embodiment, there are two independently-selected R_3 groups.

In another embodiment, there is one R_3 group.

In another embodiment, each R_3 group is methyl.

In another embodiment, there are three R_3 groups and each R_3 group is independently selected from -(C_1-C_4)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, and -(C_3-C_6)cycloalkyl.

In another embodiment, there are two R_3 groups and each R_3 group is independently selected from -(C_1-C_4)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, and -(C_3-C_6)cycloalkyl.

In another embodiment, there is one R_3 group which is -(C_1-C_4)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, or -(C_3-C_6)cycloalkyl.

In another embodiment, there are three R_3 groups and each R_3 group is independently selected from -(C_1-C_4)alkyl, -(C_2-C_6)alkenyl, and -(C_2-C_6)alkynyl.

In another embodiment, there are two R_3 groups and each R_3 group is independently selected from -(C_1-C_4)alkyl, -(C_2-C_6)alkenyl, and -(C_2-C_6)alkynyl.

In another embodiment, there is one R_3 group which is -(C_1-C_4)alkyl, -(C_2-C_6)alkenyl, or -(C_2-C_6)alkynyl.

In another embodiment, there are three R_3 groups and each R_3 group is independently selected from -(C_1-C_4)alkyl and -(C_3-C_6)cycloalkyl.

In another embodiment, there are two R_3 groups and each R_3 group is independently selected from -(C_1-C_4)alkyl and -(C_3-C_6)cycloalkyl.

In another embodiment, there is one R_3 group which is -(C_1-C_4)alkyl or -(C_3-C_6)cycloalkyl.

In another embodiment, there are three R_3 groups and each R_3 group is independently selected from -methyl, -ethyl, -n-propyl, -*iso*-propyl, -n-butyl, -*sec*-butyl, -*iso*-butyl, -*tert*-butyl, -cyclopropyl, -cyclobutyl, -cyclopentyl, and -cyclohexyl.

In another embodiment, there are three R_3 groups and each R_3 group is independently selected from -methyl, -ethyl, -n-propyl, -*iso*-propyl, -n-butyl, -*iso*-butyl, -*tert*-butyl, -cyclopropyl, -cyclobutyl, -cyclopentyl, and -cyclohexyl.

In another embodiment, there are three R_3 groups and each R_3 group is independently selected from -methyl, -ethyl, -n-propyl, -*iso*-propyl, -*iso*-butyl, -*tert*-butyl, -cyclobutyl, -cyclopentyl, and -cyclohexyl.

In another embodiment, there are three R_3 groups and each R_3 group is independently selected from -methyl, -ethyl, -*tert*-butyl, -cyclobutyl, -cyclopentyl, and -cyclohexyl.

In another embodiment, there are three R_3 groups and each R_3 group is independently selected from -methyl, -ethyl, -n-propyl, -*iso*-propyl, -n-butyl, -*sec*-butyl, -*iso*-butyl, and -*tert*-butyl.

In another embodiment, there are three R_3 groups and each R_3 group is independently selected from -methyl, -ethyl, -n-propyl, -*iso*-propyl, -n-butyl, -*iso*-butyl, and -*tert*-butyl.

In another embodiment, there are three R_3 groups and each R_3 group is independently selected from -methyl, -ethyl, -*iso*-propyl, -*iso*-butyl, and -*tert*-butyl.

In another embodiment, there are three R_3 groups and each R_3 group is independently selected from -methyl and -ethyl

In another embodiment, there are three R_3 groups each of which is -methyl.

In another embodiment, there are three R_3 groups and each R_3 group is independently selected from -cyclopropyl, -cyclobutyl, -cyclopentyl, and -cyclohexyl.

In another embodiment, there are three R_3 groups and each R_3 group is independently selected from -cyclobutyl, -cyclopentyl, and -cyclohexyl.

In another embodiment, there are two R_3 groups and each R_3 group is independently selected from -methyl, -ethyl, -n-propyl, -*iso*-propyl, -n-butyl, -*sec*-butyl, -*iso*-butyl, -*tert*-butyl, -cyclopropyl, -cyclobutyl, -cyclopentyl, and -cyclohexyl.

In another embodiment, there are two R_3 groups and each R_3 group is independently selected from -methyl, -ethyl, -n-propyl, -*iso*-propyl, -n-butyl, -*iso*-butyl, -*tert*-butyl, -cyclopropyl, -cyclobutyl, -cyclopentyl, and -cyclohexyl.

In another embodiment, there are two R_3 groups and each R_3 group is independently selected from -methyl, -ethyl, -n-propyl, -*iso*-propyl, -*iso*-butyl, -*tert*-butyl, -cyclobutyl, -cyclopentyl, and -cyclohexyl.

In another embodiment, there are two R_3 groups and each R_3 group is independently selected from -methyl, -ethyl, -*tert*-butyl, -cyclobutyl, -cyclopentyl, and -cyclohexyl.

In another embodiment, there are two R_3 groups and each R_3 group is independently selected from -methyl, -ethyl, -n-propyl, -*iso*-propyl, -n-butyl, -*sec*-butyl, -*iso*-butyl, and -*tert*-butyl.

In another embodiment, there are two R_3 groups and each R_3 group is independently selected from -methyl, -ethyl, -n-propyl, -*iso*-propyl, -n-butyl, -*iso*-butyl, and -*tert*-butyl.

In another embodiment, there are two R_3 groups and each R_3 group is independently selected from -methyl, -ethyl, -*iso*-propyl, -*iso*-butyl, and -*tert*-butyl.

In another embodiment, there are two R_3 groups and each R_3 group is independently selected from -methyl and -ethyl

In another embodiment, there are two R_3 groups each of which is -methyl.

In another embodiment, there are two R_3 groups and each R_3 group is independently selected from -cyclopropyl, -cyclobutyl, -cyclopentyl, and -cyclohexyl.

In another embodiment, there are two R_3 groups and each R_3 group is independently selected from -cyclobutyl, -cyclopentyl, and -cyclohexyl.

In another embodiment, there is one R_3 group which is -methyl, -ethyl, -n-propyl, -*iso*-propyl, -n-butyl, -*sec*-butyl, -*iso*-butyl, -*tert*-butyl, -cyclopropyl, -cyclobutyl, -cyclopentyl, or -cyclohexyl.

In another embodiment, there is one R_3 group which is -methyl, -ethyl, -n-propyl, -*iso*-propyl, -n-butyl, -*iso*-butyl, -*tert*-butyl, -cyclopropyl, -cyclobutyl, -cyclopentyl, or -cyclohexyl.

In another embodiment, there is one R_3 group which is -methyl, -ethyl, -n-propyl, -*iso*-propyl, -*iso*-butyl, -*tert*-butyl, -cyclobutyl, -cyclopentyl, or -cyclohexyl.

In another embodiment, there is one R_3 group which is -methyl, -ethyl, -*tert*-butyl, -cyclobutyl, -cyclopentyl, or -cyclohexyl.

In another embodiment, there is one R_3 group which is -methyl, -ethyl, -n-propyl, -*iso*-propyl, -n-butyl, -*sec*-butyl, -*iso*-butyl, or -*tert*-butyl.

In another embodiment, there is one R_3 group which is -methyl, -ethyl, -n-propyl, -*iso*-propyl, -n-butyl, -*iso*-butyl, or -*tert*-butyl.

In another embodiment, there is one R_3 group which is -methyl, -ethyl, -*iso*-propyl, -*iso*-butyl, or -*tert*-butyl.

In another embodiment, there is one R_3 group which is -cyclopropyl, -cyclobutyl, -cyclopentyl, or -cyclohexyl.

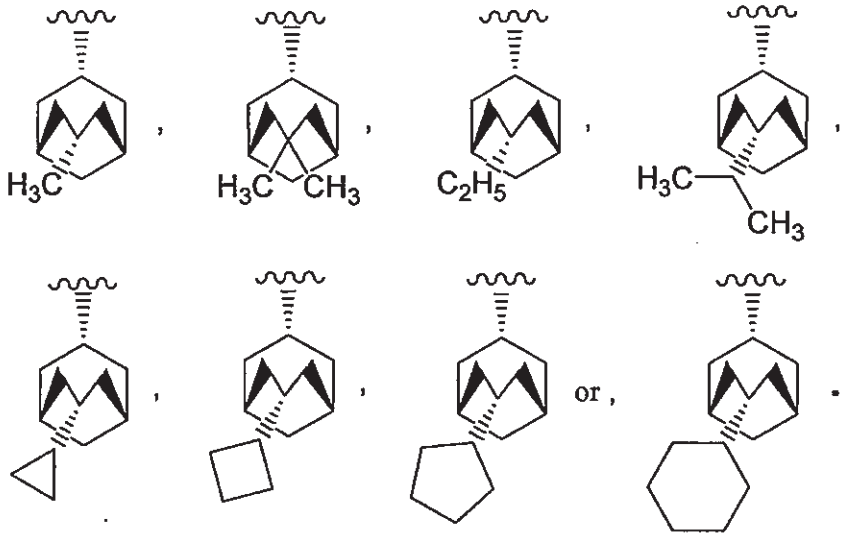
In another embodiment, there is one R_3 group which is -cyclobutyl, -cyclopentyl, or -cyclohexyl.

In another embodiment, there is one R_3 group which is -ethyl.

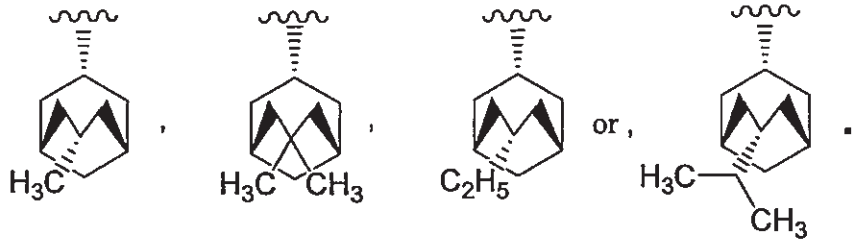
In another embodiment, there is one R_3 group which is -methyl.

In another embodiment, the carbon atom of the R_1 group which is attached to the nitrogen atom of the bridged piperidine is unsubstituted by a R_3 group.

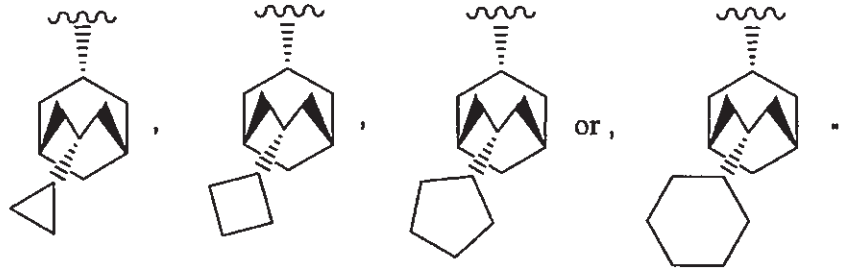
In another embodiment, R_1 and R_3 together are:



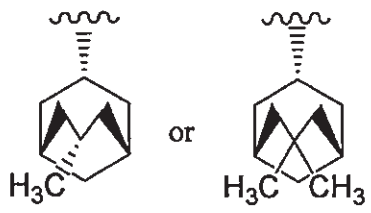
In another embodiment, R_1 and R_3 together are:



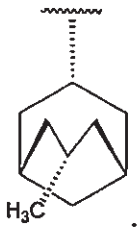
In another embodiment, R_1 and R_3 together are:



In another embodiment, R_1 and R_3 together are:



In another embodiment, R_1 and R_3 together are:



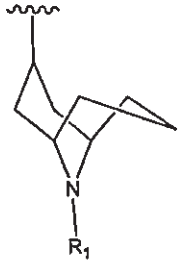
In another embodiment, R_1 is -(C_9-C_{12})cycloalkyl.

In another embodiment, R_1 is -cycloundecyl.

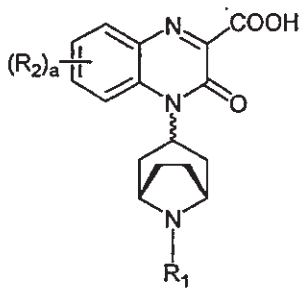
In another embodiment, b is 0, *e.g.*, for a Substituted-Quinoxaline-Type Bridged-Piperidine Compound where each R_5 is -H, the bridged piperidine is:



In another embodiment, b is 1, *e.g.*, for a Substituted-Quinoxaline-Type Bridged-Piperidine Compound where each R_5 is -H, the bridged piperidine is:



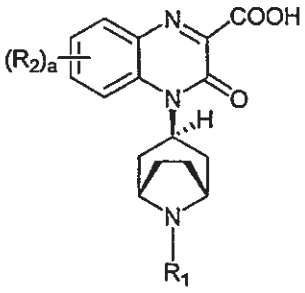
In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (I'A) is a Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (I'B):



(I'B)

wherein R_1, R_2, and a are as defined above for the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of Formula (I').

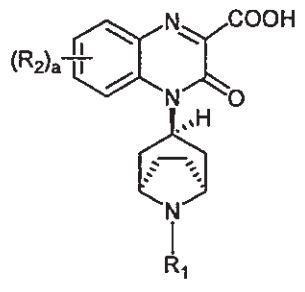
In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (I'A) is a Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (I'B1):



(I'B1)

i.e., a Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (I'B) wherein the 6-membered, nitrogen-containing ring that is fused to the benzo is in the *endo*- conformation with respect to the (-CH_2-CH_2-) bridge of the bridged piperidine.

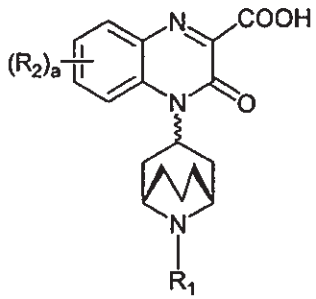
In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (I'A) is a Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (I'B2):



(I'B2)

i.e., a Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (I'B) wherein the 6-membered, nitrogen-containing ring that is fused to the benzo is in the *exo*- conformation with respect to the (-CH_2-CH_2-) bridge of the bridged piperidine.

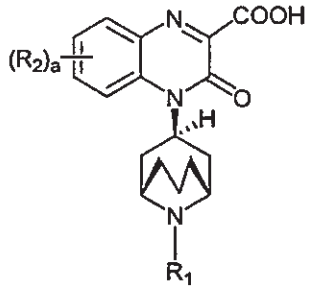
In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (I'A) is a Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (I'C):



(I'C)

wherein R_1, R_2, and a are as defined above for the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of Formula (I').

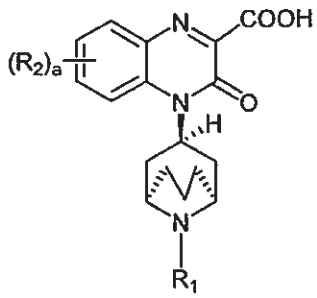
In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (I'A) is a Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (I'C1):



(I'C1)

i.e., a Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (I'C) wherein the 6-membered, nitrogen-containing ring that is fused to the benzo is in the *endo*- conformation with respect to the (-CH_2-CH_2-CH_2-) bridge of the bridged piperidine.

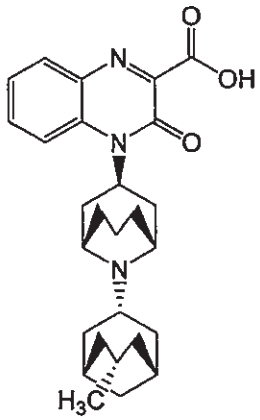
In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (I'A) is a Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (I'C2):



(I'C2)

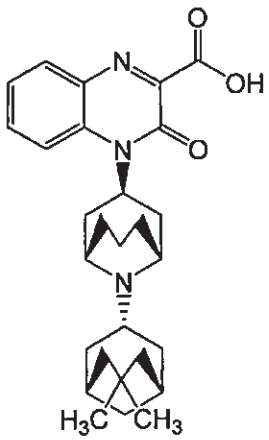
i.e., a Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (I'C) wherein the 6-membered, nitrogen-containing ring that is fused to the benzo is in the *exo*- conformation with respect to the (-CH_2-CH_2-CH_2-) bridge of the bridged piperidine.

In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound is:



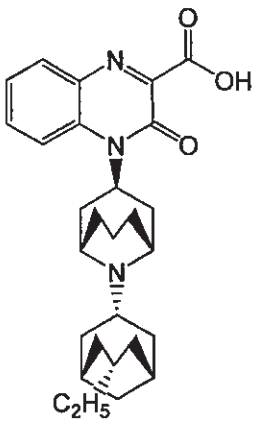
or a pharmaceutically acceptable derivative thereof.

In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound is:



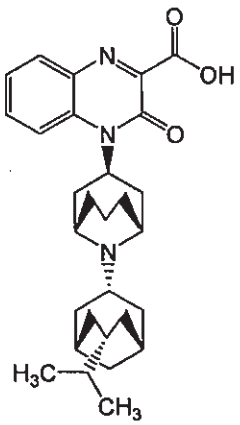
or a pharmaceutically acceptable derivative thereof.

In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound is:



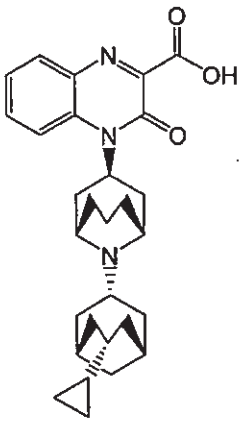
or a pharmaceutically acceptable derivative thereof.

In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound is:



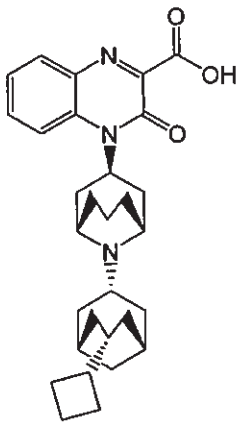
or a pharmaceutically acceptable derivative thereof.

In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound is:



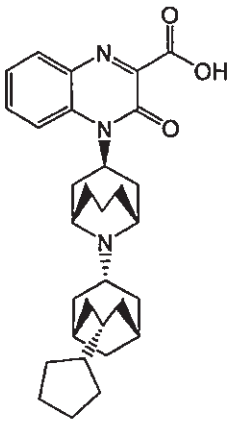
or a pharmaceutically acceptable derivative thereof.

In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound is:



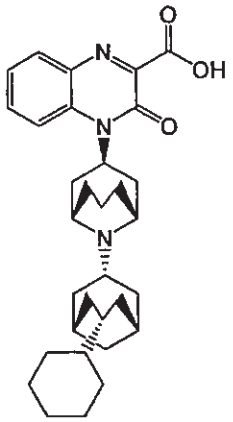
or a pharmaceutically acceptable derivative thereof.

In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound is:



or a pharmaceutically acceptable derivative thereof.

In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound is:



or a pharmaceutically acceptable derivative thereof.

In another embodiment, the pharmaceutically acceptable derivative is a hydrate.

In another embodiment, the pharmaceutically acceptable derivative is a pharmaceutically acceptable salt.

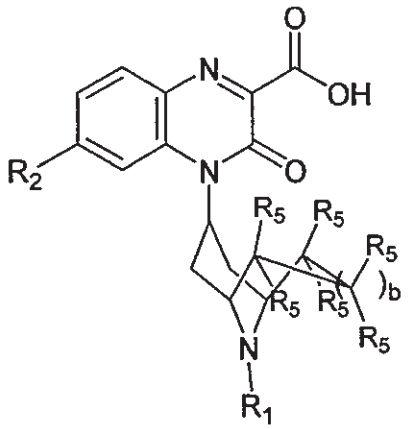
In another embodiment, the pharmaceutically acceptable salt is a *p*-toluenesulfonic acid salt, a sulfate salt, a phosphoric acid salt, or a hydrochloride salt.

In another embodiment, the pharmaceutically acceptable salt is a *p*-toluenesulfonic acid salt, a sulfate salt, or a phosphoric acid salt.

In another embodiment, the pharmaceutically acceptable salt is a *p*-toluenesulfonic acid salt.

4.3 Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of Formula (II)

As stated above, the invention encompasses Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of Formula (II):



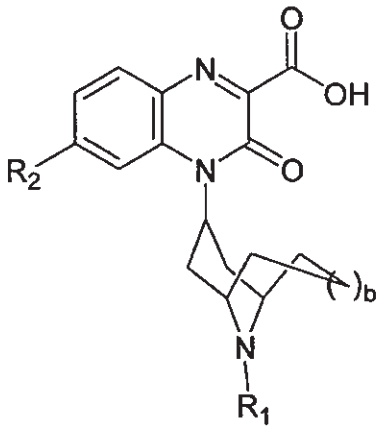
(II)

or a pharmaceutically acceptable derivative thereof where R_1, R_2, R_5, and b are defined above for the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of Formulae (I) or (I').

In one embodiment, each R_5 is independently selected from -H, -(C_1-C_3)alkyl, -C(halo)$_3$, or -halo.

In another embodiment, each R_5 is independently selected from -H, -CH_3, -CF_3, or -F.

In another embodiment, each R_5 is -H, *i.e.*, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound is a compound of Formula (IIA):



(IIA)

or a pharmaceutically acceptable derivative thereof where R_1, R_2, and b are defined above for the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of Formula (II).

In another embodiment, R_2 is -halo.

In another embodiment, R_2 is -F.

In another embodiment, the 3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid portion of the Substituted-Quinoxaline-Type Bridged-Piperidine Compound is in the *endo-* or *exo-* conformation with respect to the bridge of the bridged piperidine.

In another embodiment, the 3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid portion of the Substituted-Quinoxaline-Type Bridged-Piperidine Compound is in the *endo-* conformation with respect to the bridge of the bridged piperidine.

In another embodiment, the 3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid portion of the Substituted-Quinoxaline-Type Bridged-Piperidine Compound is in the *exo-* conformation with respect to the bridge of the bridged piperidine.

In another embodiment, R_1 is -(C_9-C_{12})cycloalkyl or -(C_9-C_{12})bicycloalkyl.

In another embodiment, R_1 is -(C_9-C_{12})bicycloalkyl.

In another embodiment, R_1 is bicyclo[3.3.1]nonyl.

In another embodiment, R_1 is 1-bicyclo[3.3.1]nonyl, 2-bicyclo[3.3.1]nonyl, or 3-bicyclo[3.3.1]nonyl.

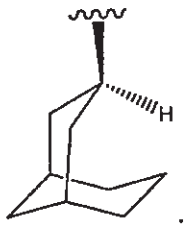
In another embodiment, R_1 is not 9-bicyclo[3.3.1]nonyl.

In another embodiment, R_1 is in the *endo-* or *exo-* conformation with respect to the bridge of the bridged piperidine.

In another embodiment, R_1 is in the *endo-* conformation with respect to the bridge of the bridged piperidine.

In another embodiment, R_1 is in the *exo-* conformation with respect to the bridge of the bridged piperidine.

In another embodiment, R_1 is:



In another embodiment, R_1 is -(C_9-C_{12})cycloalkyl.

In another embodiment, R_1 is -cycloundecyl.

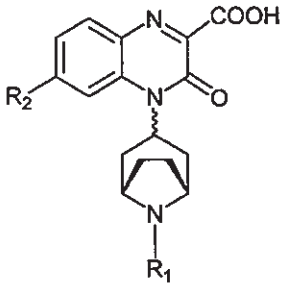
In another embodiment, b is 0, *e.g.*, for a Substituted-Quinoxaline-Type Bridged-Piperidine Compound where each R_5 is -H, the bridged piperidine is:



In another embodiment, b is 1, *e.g.*, for a Substituted-Quinoxaline-Type Bridged-Piperidine Compound where each R_5 is -H, the bridged piperidine is:



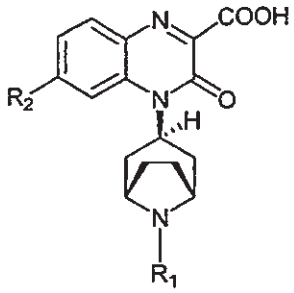
In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (IIA) is a Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (IIB):



(IIB)

wherein R_1 and R_2 are as defined above for the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of Formula (II).

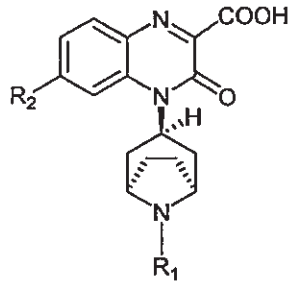
In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (IIA) is a Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (IIB1):



(IIB1)

i.e., a Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (IIB) wherein the 6-membered, nitrogen-containing ring that is fused to the benzo is in the *endo*- conformation with respect to the (-CH_2-CH_2-) bridge of the bridged piperidine.

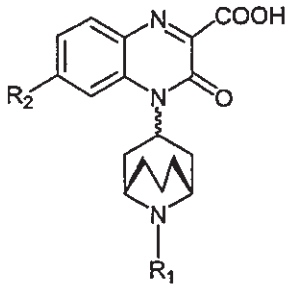
In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (IIA) is a Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (IIB2):



(IIB2)

i.e., a Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (IIB) wherein the 6-membered, nitrogen-containing ring that is fused to the benzo is in the *exo*- conformation with respect to the (-CH_2-CH_2-) bridge of the bridged piperidine.

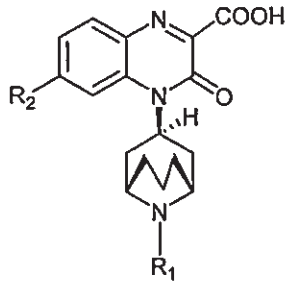
In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (IIA) is a Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (IIC):



(IIC)

wherein R_1 and R_2 are as defined above for the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of Formula (II).

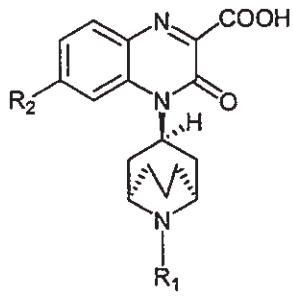
In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (IIA) is a Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (IIC1):



(IIC1)

i.e., a Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (IIC) wherein the 6-membered, nitrogen-containing ring that is fused to the benzo is in the *endo*- conformation with respect to the (-CH_2-CH_2-CH_2-) bridge of the bridged piperidine.

In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (IIA) is a Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (IIC2):



(IIC2)

i.e., a Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (IIC) wherein the 6-membered, nitrogen-containing ring that is fused to the benzo is in the *exo*- conformation with respect to the (-CH_2-CH_2-CH_2-) bridge of the bridged piperidine.

In another embodiment, the pharmaceutically acceptable derivative is a hydrate.

In another embodiment, the pharmaceutically acceptable derivative is a pharmaceutically acceptable salt.

In another embodiment, the pharmaceutically acceptable salt is a *p*-toluenesulfonic acid salt, a sulfate salt, a phosphoric acid salt, or a hydrochloride salt.

In another embodiment, the pharmaceutically acceptable salt is a *p*-toluenesulfonic acid salt, a sulfate salt, or a phosphoric acid salt.

In another embodiment, the pharmaceutically acceptable salt is a *p*-toluenesulfonic acid salt.

4.4 Definitions

As used in connection with the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds herein, the terms used herein having following meaning:

"-(C_1-C_4)alkyl" means a straight chain or branched non-cyclic hydrocarbon having from 1 to 4 carbon atoms. Representative straight chain -(C_1-C_4)alkyls include -methyl, -ethyl, -n-propyl, and -n-butyl. Representative branched -(C_1-C_4)alkyls include -*iso*-propyl, -*sec*-butyl, -*iso*-butyl, and -*tert*-butyl.

"-(C_1-C_3)alkyl" means a straight chain or branched non-cyclic hydrocarbon having from 1 to 3 carbon atoms. Representative straight chain -(C_1-C_3)alkyls include -methyl, -ethyl, and -n-propyl. Representative branched -(C_1-C_3)alkyls include -*iso*-propyl.

"-(C_2-C_6)alkenyl" means a straight chain or branched non-cyclic hydrocarbon having from 2 to 6 carbon atoms and including at least one carbon-carbon double bond. Representative straight chain and branched (C_2-C_6)alkenyls include -vinyl, -allyl, -1-butenyl, -2-butenyl, -*iso*-butylenyl, -1-pentenyl, -2-pentenyl, -3-methyl-1-butenyl, -2-methyl-2-butenyl, -2,3-dimethyl-2-butenyl, -1-hexenyl, 2-hexenyl, 3-hexenyl, and the like.

"-(C_2-C_6)alkynyl" means a straight chain or branched non-cyclic hydrocarbon having from 2 to 6 carbon atoms and including at least one carbon-carbon triple bond. Representative straight chain and branched (C_2-C_6)alkynyls include -acetylenyl, -propynyl, -1-butynyl, -2-butynyl, -1-pentynyl, -2-pentynyl, -3-methyl-1-butynyl, -4-pentynyl, -1-hexynyl, -2-hexynyl, -5-hexynyl, and the like.

"-(C_9-C_{14})cycloalkyl" means a saturated monocyclic hydrocarbon having from 9 to 14 carbon atoms. Representative (C_9-C_{14})cycloalkyls are -cyclononyl, -cyclodecyl, -cycloundecyl, -cyclododecyl, -cyclotridecyl, and -cyclotetradecyl.

"-(C_{11}-C_{14})cycloalkyl" means a saturated monocyclic hydrocarbon having from 11 to 14 carbon atoms. Representative (C_{11}-C_{14})cycloalkyls are -cycloundecyl, -cyclododecyl, -cyclotridecyl, and -cyclotetradecyl.

"-(C_9-C_{12})cycloalkyl" means a saturated monocyclic hydrocarbon having from 9 to 12 carbon atoms. Representative (C_9-C_{12})cycloalkyls are -cyclononyl, -cyclodecyl, -cycloundecyl, and -cyclododecyl.

"-(C_3-C_6)cycloalkyl" means a saturated monocyclic hydrocarbon having from 3 to 6 carbon atoms. Representative (C_3-C_6)cycloalkyls include -cyclopropyl, -cyclobutyl, -cyclopentyl, and -cyclohexyl.

"-(C_9-C_{14})bicycloalkyl" means a bi-cyclic hydrocarbon ring system having from 9 to 14 carbon atoms and at least one saturated cyclic alkyl ring. Representative -(C_9-C_{14})bicycloalkyls include -indanyl, -bicyclo[3.3.1]nonyl, such as -1-bicyclo[3.3.1]nonyl, -2-bicyclo[3.3.1]nonyl, -3-bicyclo[3.3.1]nonyl and -9-bicyclo[3.3.1]nonyl, -bicyclo[4.2.1]nonyl, -1,2,3,4-tetrahydronaphthalenyl, -5,6,7,8-tetrahydronaphthalenyl, -perhydronaphthalenyl, -bicyclo[3.3.2]decyl, -bicyclo[4.2.2]decyl, -bicyclo[4.3.1]decyl, -bicyclo[3.3.3]undecyl, -bicyclo[4.3.2]undecyl, -bicyclo[6.2.1]undecyl, -bicyclo[4.3.3]dodecyl, -bicyclo[6.3.1]dodecyl, -bicyclo[6.3.1]dodeca-8,10-dienyl, -bicyclo[7.3.1]tridecyl, -bicyclo[7.2.2]tridecyl, -bicyclo[7.2.2]trideca-1(11),9-dienyl, -bicyclo[9.1.1]tridecyl, -bicyclo[8.2.1]tridecyl, -bicyclo[7.3.2]tetradecyl, -bicyclo[8.3.1]tetradecyl, and the like.

"-(C_9-C_{12})bicycloalkyl" means a bi-cyclic hydrocarbon ring system having from 9 to 12 carbon atoms and at least one saturated cyclic alkyl ring. Representative -(C_9-C_{12})bicycloalkyls include -indanyl, -bicyclo[3.3.1]nonyl, such as -1-bicyclo[3.3.1]nonyl, -2-bicyclo[3.3.1]nonyl, -3-bicyclo[3.3.1]nonyl and -9-bicyclo[3.3.1]nonyl, -bicyclo[4.2.1]nonyl, -1,2,3,4-tetrahydronaphthalenyl, -5,6,7,8-tetrahydronaphthalenyl, -perhydronaphthalenyl, -bicyclo[3.3.2]decyl, -bicyclo[4.2.2]decyl, -bicyclo[4.3.1]decyl, -bicyclo[3.3.3]undecyl, -bicyclo[4.3.2]undecyl, -bicyclo[6.2.1]undecyl, -bicyclo[4.3.3]dodecyl, -bicyclo[6.3.1]dodecyl, -bicyclo[6.3.1]dodeca-8,10-dienyl, and the like.

"-(C_{10}-C_{14})bicycloalkyl" means a bi-cyclic hydrocarbon ring system having from 10 to 14 carbon atoms and at least one saturated cyclic alkyl ring. Representative -(C_{10}-C_{14})bicycloalkyls include -1,2,3,4-tetrahydronaphthalenyl, -5,6,7,8-tetrahydronaphthalenyl, -perhydronaphthalenyl, -bicyclo[3.3.2]decyl, -bicyclo[4.2.2]decyl, -bicyclo[4.3.1]decyl, -bicyclo[3.3.3]undecyl, -bicyclo[4.3.2]undecyl, -bicyclo[6.2.1]undecyl, -bicyclo[4.3.3]dodecyl, -bicyclo[6.3.1]dodecyl, -

bicyclo[6.3.1]dodeca-8,10-dienyl, -bicyclo[7.3.1]tridecyl, -bicyclo[7.2.2]tridecyl, -bicyclo[7.2.2]trideca-1(11),9-dienyl, -bicyclo[9.1.1]tridecyl, -bicyclo[8.2.1]tridecyl, -bicyclo[7.3.2]tetradecyl, -bicyclo[8.3.1]tetradecyl, and the like.

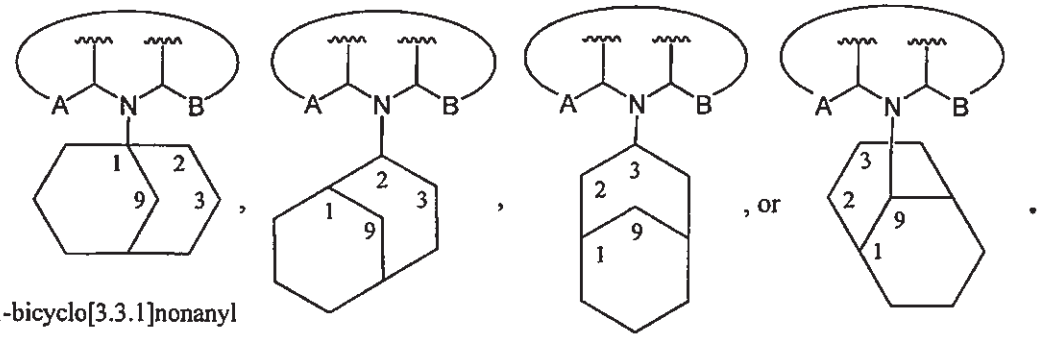
"-C(halo)$_3$" means a methyl group where each of the hydrogens of the methyl group has been replaced with a halogen. Representative -C(halo)$_3$ groups include -CF_3, -CCl_3, -CBr_3, and -CI_3.

"-Halogen" or "-halo" means -F, -Cl, -Br, or -I.

"Oxo", "=O", and the like as used herein mean an oxygen atom doubly bonded to carbon or another element.

"(C_2-C_3)bridge" as used herein means a hydrocarbon chain containing 2 or 3 carbon atoms joining the carbon atoms at positions 2 and 6 of the piperidine ring; for simplicity in some chemical structures herein A and B are illustrated as substituents of the piperidine ring with the understanding that A-B together form the (C_2-C_3)bridge. Exemplary compounds of the invention include those with an unsubstituted (C_2)bridge, *i.e.*, -CH_2-CH_2-, joining positions 2 and 6 of the piperidine ring (A-B together form an unsubstituted (C_2)bridge) and an unsubstituted (C_3)bridge, *i.e.*, -CH_2-CH_2-CH_2-, joining positions 2 and 6 of the piperidine ring (A-B together form an unsubstituted (C_3)bridge). Examples of compounds where A-B can together form a (C_2-C_3)bridge include compounds comprising the following ring systems: 8-aza-bicyclo[3.2.1]octane and 9-aza-bicyclo[3.3.1]nonane.

In compounds of the invention comprising bicyclo[3.3.1]nonyl as R_1, the bicyclo[3.3.1]nonyl can be attached to the nitrogen atom of the bridged piperidine in the following ways:



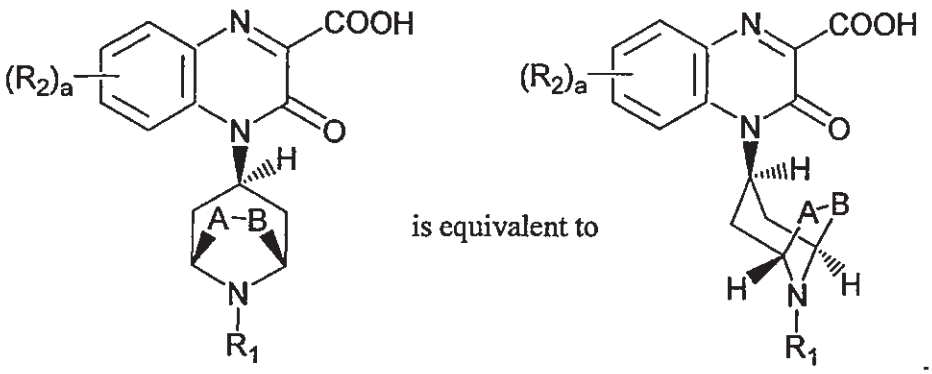
1-bicyclo[3.3.1]nonanyl

2-bicyclo[3.3.1]nonanyl

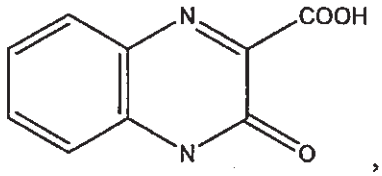
3-bicyclo[3.3.1]nonanyl

9-bicyclo[3.3.1]nonanyl

In compounds of the invention, the exemplary *endo* bridge

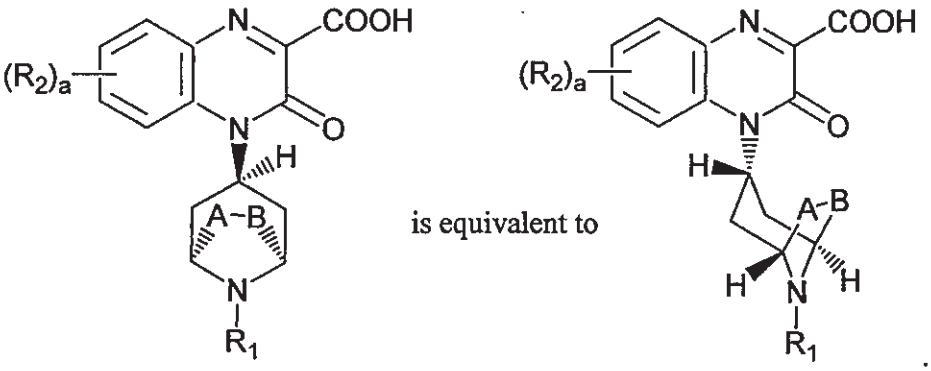


In such *endo*-compounds, the 3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid portion of the compound, *i.e.*:



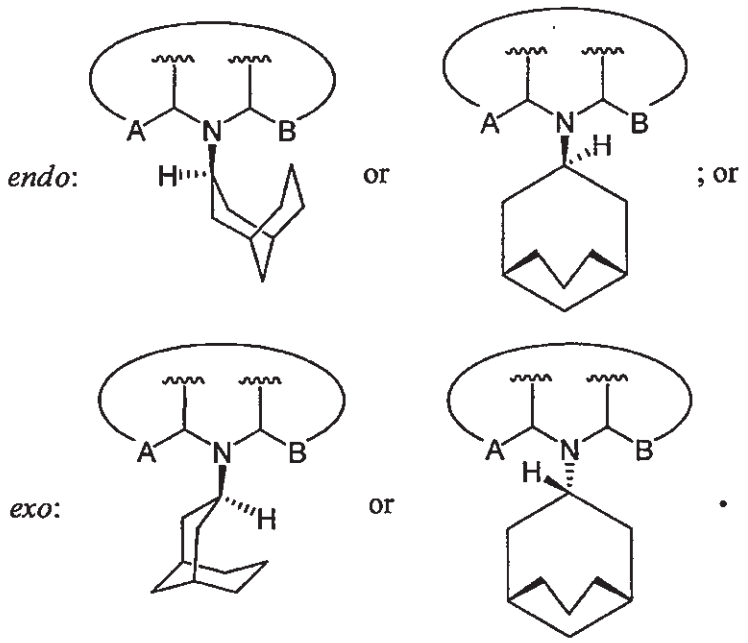
is in the *endo*- conformation with respect to the bridge of the bridged piperidine.

In compounds of the invention, the exemplary *exo* bridge



In such *exo*-compounds, the 3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid portion of the compound is in the *exo*- conformation with respect to the bridge of the bridged piperidine.

In compounds of the invention where the -R_1 group comprises a bicyclic group, that bicyclic group can have two orientations. For example, for a -R_1 group that is a -(C_9-C_{14})bicycloalkyl, *e.g.*, bicyclo[3.3.1]nonyl, attached directly to the piperidine ring nitrogen, the following orientations are possible:



In such *endo*-compounds, the -R_1 group of the compound is in the *endo*- conformation with respect to the bridge of the bridged piperidine. In such *exo*-compounds, the -R_1 group of the compound is in the *exo*- conformation with respect to the bridge of the bridged piperidine.

When a first group is "substituted with one or more" second groups, one or more hydrogen atoms of the first group is replaced with a corresponding number of second groups. When the number of second groups is two or greater, each second group can be the same or different.

In one embodiment, a first group is substituted with up to three second groups.

In another embodiment, a first group is substituted with one or two second groups.

In another embodiment, a first group is substituted with only one second group.

The term "animal" includes, but is not limited to, a human or a non-human animal, such as a companion animal or livestock, *e.g.*, a cow, monkey, baboon, chimpanzee, horse, sheep, pig, chicken, turkey, quail, cat, dog, mouse, rat, rabbit or guinea pig.

The phrase "pharmaceutically acceptable derivative", as used herein, includes any pharmaceutically acceptable salt, solvate, prodrug, radiolabeled, stereoisomer, enantiomer, diastereomer, other stereoisomeric form, racemic mixture, geometric isomer, and/or tautomer, *e.g.*, of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound of the invention. In one embodiment, the pharmaceutically acceptable derivative is a pharmaceutically acceptable salt, solvate, radiolabeled, stereoisomer, enantiomer, diastereomer, other stereoisomeric form, racemic mixture, geometric isomer, and/or tautomer, *e.g.*, of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound of the invention. In another embodiment, the pharmaceutically acceptable

derivative is a pharmaceutically acceptable salt, *e.g.*, of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound of the invention.

The phrase "pharmaceutically acceptable salt", as used herein, is any pharmaceutically acceptable salt that can be prepared from a Substituted-Quinoxaline-Type Bridged-Piperidine Compound including a salt formed from an acid and a basic functional group, such as a nitrogen group, of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound. Illustrative salts include, but are not limited, to sulfate, citrate, acetate, trifluoroacetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucoronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, and pamoate (*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. The term "pharmaceutically acceptable salt" also includes a salt prepared from a Substituted-Quinoxaline-Type Bridged-Piperidine Compound having an acidic functional group, such as a carboxylic acid functional group, and a pharmaceutically acceptable inorganic or organic base. Suitable bases include, but are not limited to, hydroxides of alkali metals such as sodium, potassium, cesium, and lithium; hydroxides of alkaline earth metal such as calcium and magnesium; hydroxides of other metals, such as aluminum and zinc; ammonia and organic amines, such as unsubstituted or hydroxy-substituted mono-, di-, or trialkylamines; dicyclohexylamine; tributyl amine; pyridine; picoline; N-methyl, N-ethylamine; diethylamine; triethylamine; mono-, bis-, or tris-(2-hydroxy-(C_1-C_3)alkyl amines), such as mono-, bis-, or tris-(2-hydroxyethyl)amine, 2-hydroxy-*tert*-butylamine, or tris-(hydroxymethyl)methylamine, N,N-di-[(C_1-C_3)alkyl] -N-(hydroxy-(C_1-C_3)alkyl)-amines, such as N,N-dimethyl-N-(2-hydroxyethyl)amine, or tri-(2-hydroxyethyl)amine; N-methyl-D-glucamine; and amino acids such as arginine, lysine, and the like. One skilled in the art will recognize that, *e.g.*, acid addition salts of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound can be prepared by reaction of the compounds with the appropriate acid via a variety of known methods.

The invention disclosed herein is also meant to encompass all solvates of the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds. "Solvates" are known in the art and are considered to be a combination, physical association and/or solvation of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound with a solvent molecule, *e.g.*, a disolvate, monosolvate or hemisolvate when the solvent molecule: Substituted-Quinoxaline-Type Bridged-Piperidine Compound molecule ratio is 2:1, 1:1 or 1:2, respectively. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances, the solvate can be isolated, for example when one or more solvent molecules are incorporated into the crystal lattice of a crystalline solid. Thus, "solvate", as used herein, encompasses both solution-phase and isolatable solvates. A Substituted-Quinoxaline-Type Bridged-Piperidine Compound of

the invention can be present as a solvated form with a pharmaceutically acceptable solvent, such as water, methanol, ethanol, and the like, and it is intended that the invention include both solvated and unsolvated Substituted-Quinoxaline-Type Bridged-Piperidine Compound forms. As "hydrate" relates to a particular subgroup of solvates, *i.e.*, where the solvent molecule is water, hydrates are included within the solvates of the invention. Preparation of solvates is known in the art. For example, M. Caira *et al.*, *J. Pharmaceut. Sci.*, 93(3):601-611 (2004), describes the preparation of solvates of fluconazole with ethyl acetate and with water. Similar preparations of solvates, hemisolvate, hydrates, and the like are described by E.C. van Tonder *et al.*, *AAPS Pharm. Sci. Tech.*, 5(1):Article 12 (2004), and A.L. Bingham *et al.*, *Chem. Commun.*, 603-604 (2001). A typical, non-limiting, process involves dissolving the Substituted-Quinoxaline-Type Bridged-Piperidine Compound in a desired amount of the desired solvent (organic, water or mixtures thereof) at temperatures above about 20°C to about 25°C, cooling the solution at a rate sufficient to form crystals, and isolating the crystals by known methods, *e.g.*, filtration. Analytical techniques, for example, infrared spectroscopy, can be used to show the presence of the solvent in a crystal of the solvate.

The invention disclosed herein is also meant to encompass all prodrugs of the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds. "Prodrugs" are known in the art and, while not necessarily possessing any pharmaceutical activity as such, are considered to be any covalently bonded carrier(s) that releases the active parent drug *in vivo*. In general, such prodrugs will be a functional derivative of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (I), Formula (I') or Formula (II) which is readily convertible *in vivo*, *e.g.*, by being metabolized, into the required Substituted-Quinoxaline-Type Bridged-Piperidine Compound of Formula (I), Formula (I') or Formula (II). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described in, for example, *Design of Prodrugs*, H. Bundgaard ed., Elsevier (1985); "Drug and Enzyme Targeting, Part A," K. Widder *et al.* eds., Vol. 112 in *Methods in Enzymology*, Academic Press (1985); Bundgaard, "Design and Application of Prodrugs," Chapter 5 (pp. 113-191) in *A Textbook of Drug Design and Development*, P. Krogsgaard-Larsen and H. Bundgaard eds., Harwood Academic Publishers (1991); Bundgaard *et al.*, *Adv. Drug Delivery Revs.* 8:1-38 (1992); Bundgaard *et al.*, *J. Pharmaceut. Sci.* 77:285 (1988); and Kakeya *et al.*, *Chem. Pharm. Bull.* 32:692 (1984).

In addition, one or more hydrogen, carbon or other atoms of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound can be replaced by an isotope of the hydrogen, carbon or other atoms. Such a "radiolabeled", "radiolabeled form", and the like of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound, each of which is encompassed by the invention, is useful as a research and/or diagnostic tool in metabolism pharmacokinetic studies and in binding assays. Examples of isotopes that can be incorporated into a Substituted-Quinoxaline-Type Bridged-

Piperidine Compound of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. Radiolabeled compounds of the invention can be prepared by methods known in the art. For example, tritiated compounds of Formula I can be prepared by introducing tritium into the particular compound of Formula I, for example, by catalytic dehalogenation with tritium. This method can include reacting a suitably halogen-substituted precursor of a compound of Formula (I), Formula (I') or Formula (II) with tritium gas in the presence of a suitable catalyst, for example, Pd/C, in the presence or absence of a base. Other suitable methods for preparing tritiated compounds can be found in Filer, *Isotopes in the Physical and Biomedical Sciences, Vol. 1, Labeled Compounds (Part A)*, Chapter 6 (1987). ^{14}C-labeled compounds can be prepared by employing starting materials having a ^{14}C carbon.

A Substituted-Quinoxaline-Type Bridged-Piperidine Compound can contain one or more asymmetric centers and can thus give rise to enantiomers, diastereomers, and other stereoisomeric forms. The invention is also meant to encompass all such possible forms as well as their racemic and resolved forms or any mixture thereof. When a Substituted-Quinoxaline-Type Bridged-Piperidine Compound contains an olefinic double bond or other center of geometric asymmetry, and unless specified otherwise, it is intended to include all "geometric isomers", *e.g.*, both E and Z geometric isomers. All "tautomers", *e.g.*, ketone-enol, amide-imidic acid, lactam-lactim, enamine-imine, amine-imine, and enamine-enimine tautomers, are intended to be encompassed by the invention as well.

As used herein, the terms "stereoisomer", "stereoisomeric form", and the like are general terms for all isomers of individual molecules that differ only in the orientation of their atoms in space. It includes enantiomers and isomers of compounds with more than one chiral center that are not mirror images of one another ("diastereomers").

The term "chiral center" refers to a carbon atom to which four different groups are attached.

The term "enantiomer" or "enantiomeric" refers to a molecule that is nonsuperimposeable on its mirror image and hence optically active where the enantiomer rotates the plane of polarized light in one direction and its mirror image rotates the plane of polarized light in the opposite direction.

The term "racemic" refers to a mixture of equal parts of enantiomers which is optically inactive.

The term "resolution" refers to the separation or concentration or depletion of one of the two enantiomeric forms of a molecule.

Optical isomers of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound can be obtained by known techniques such as chiral chromatography or formation of diastereomeric salts from an optically active acid or base.

The phrase "effective amount", when used in connection with a Substituted-Quinoxaline-Type Bridged-Piperidine Compound, means an amount effective for: (a) treating or preventing a Condition; (b) detectably inhibiting ORL-1 receptor function in a cell; or (c) detectably activating ORL-1 receptor function in a cell.

The phrase "effective amount", when used in connection with a second therapeutic agent means an amount for providing the therapeutic effect of the therapeutic agent.

The terms "modulate", "modulating", and the like as used herein with respect to the ORL-1 receptor mean the mediation of a pharmacodynamic response (*e.g.*, analgesia) in an animal from (i) inhibiting or activating the receptor, or (ii) directly or indirectly affecting the normal regulation of the receptor activity. Compounds that modulate the receptor activity include agonists, partial agonists, antagonists, mixed agonists/antagonists, mixed partial agonists/antagonists and compounds which directly or indirectly affect regulation of the receptor activity.

As used herein, a compound that binds to a receptor and mimics the regulatory effect(s) of an endogenous ligand is defined as an "agonist". As used herein, a compound that binds to a receptor and is only partly effective as an agonist is defined as a "partial agonist". As used herein, a compounds that binds to a receptor but produces no regulatory effect, but rather blocks binding of another agent to the receptor is defined as an "antagonist". (*See* Ross and Kenakin, *Pharmacodynamics: Mechanisms of Drug Action and the Relationship Between Drug Concentration and Effect*, Chapter 2 in *Goodman & Gilman's The Pharmacological Basis of Therapeutics* 31-32 (J.G. Hardman, L.E. Limbird and A. Goodman-Gilman eds., 10th Ed. 2001).

The term "MeOH" means methanol, *i.e.*, methyl alcohol.

The term "EtOH" means ethanol, *i.e.*, ethyl alcohol.

The term "Et_2O" means diethyl ether, *i.e.*, ethoxyethane.

The term "THF" means tetrahydrofuran.

The term "DMF" means *N,N*-dimethylformamide.

The term "DCM" means methylene chloride, *i.e.*, dichloromethane or CH_2Cl_2.

The term "DCE" means dichloroethane, *i.e.*, 1,1-dichloroethane.

The term "EtOAc" means ethyl acetate.

The term "MeCN" means acetonitrile.

The term "DME" means dimethoxyethane, *i.e.*, 1,2-dimethoxyethane.

The term "DMSO" means dimethylsulfoxide, *i.e.*, methylsulfinylmethane.

The term "AcOH" means acetic acid.

The term "TEA" means triethylamine.

The term "NaH" means sodium hydride.

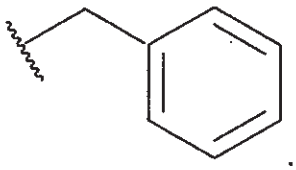
The term "TsOH" means *p*-toluene sulfonic acid, *i.e.*, toluene-4-sulfonic acid.

The term "DPPA" means diphenyl phosphorazidate, *i.e.*, diphenyl phosphoryl azide.

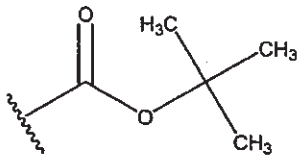
The term "TFA" means trifluoroacetic acid, *i.e.*, 2,2,2-trifluoroacetic acid.

The term "TFAA" means trifluoroacetic anhydride, *i.e.*, 2,2,2-trifluoroacetic anhydride.

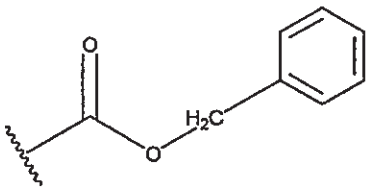
The term "Bn" means benzyl, *i.e.*



The term "BOC" means *tert*-butyloxycarbonyl, *i.e.*



The term "CBZ" means benzyloxycarbonyl, *i.e.*



The term "IBD" means inflammatory-bowel disease.

The term "IBS" means irritable-bowel syndrome.

The term "ALS" means amyotrophic lateral sclerosis.

The phrases "treatment of", "treating", and the like include the amelioration or cessation of a Condition or a symptom thereof. In one embodiment, treating includes inhibiting, for example, decreasing the overall frequency of episodes of a Condition or a symptom thereof.

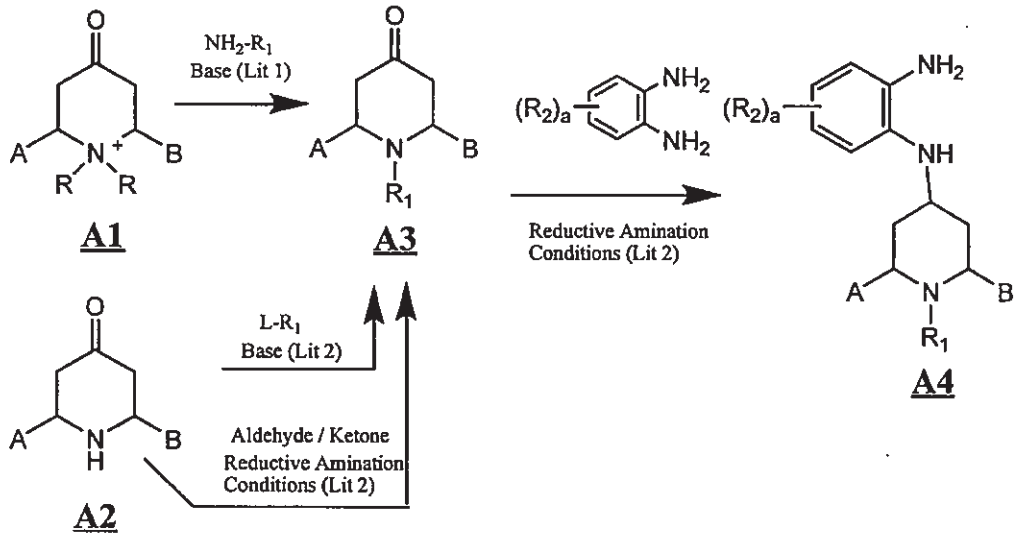
The phrases "prevention of", "preventing", and the like include the avoidance of the onset of a Condition or a symptom thereof.

A "disorder" includes, but is not limited to, the Conditions defined above.

4.5 Methods for Making the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds

The invention relates to methods for preparing Substituted-Quinoxaline-Type Bridged-Piperidine Compounds and/or pharmaceutically acceptable derivatives thereof, such as illustrated in the synthetic Schemes below. The Substituted-Quinoxaline-Type Bridged-Piperidine Compounds can be made using conventional organic synthesis, in view of the present disclosure, and including the following illustrative methods shown in the schemes below where R_1, R_2 and a are defined above, A and B are as defined in connection with a (C_2-C_3)bridge, L is a halogen leaving group such as Br or I, L' is F or Cl, and R is -(C_1-C_4)alkyl or -CF_3.

Scheme A



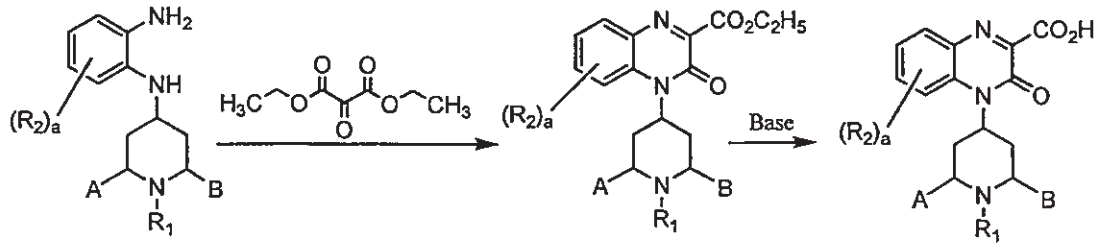
In Scheme A and the other schemes, "Lit 1" refers to the procedures described in the publications D.A. Tortolini and M. A. Poss, *Org. Lett.* 1:1261 (1999) and/or International PCT Publication No. WO 2005/075459 A1 of Euro-Celtique S.A., and "Lit 2" refers to the procedures described in U.S. Patent No. 6,635,653 by Goehring *et al.*

Compounds of formula **A1** and **A2** are commercially available or can be prepared by methods known to the art.

A piperidinium salt of structure **A1** can be reacted with a primary amine in a suitable solvent such as EtOH under reflux conditions in the presence of a base such as K_2CO_3 as described in reference "Lit 1" to provide the 1-(substituted)Bridged-Piperidine-4-one compound **A3**. As described in reference "Lit 2," compound **A3** can also be prepared by alkylation of a Bridged-

Piperidine-4-one of structure **A2** with an alkyl bromide or alkyl iodide in a suitable solvent such as DMF, MeCN or DMSO in the presence of an inorganic base such as K_2CO_3 or an organic base such as diisopropylethylamine. As described in reference "Lit 2," compound **A3** can also be prepared by reductive amination of compound **A2** with an aldehyde or ketone using either sodium triacetoxyborohydride or sodium cyanoborohydride in a suitable solvent such as DCM or MeOH, respectively. Compound **A3** can then be reductively aminated with a substituted or unsubstituted 1,2-phenylenediamine using sodium triacetoxyborohydride or sodium cyanoborohydride in a suitable solvent such as DCM or MeOH, respectively, to provide compound **A4**, as described in reference "Lit 2."

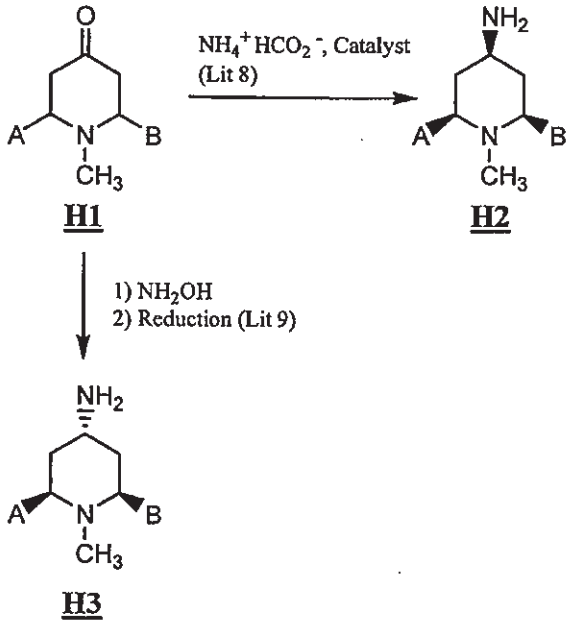
Scheme F



A4 **F1** **F2**

Compound **A4** and diethyl 2-oxomalonate can be dissolved in a solvent with a high boiling point, such as toluene or xylene, and heated under reflux conditions with azeotropic removal of water to provide compound **F1**. Compound **F1** can be hydrolyzed to the carboxylic acid **F2** by treatment with a base, such as aqueous NaOH, in a solvent under appropriate conditions, such as MeOH or EtOH at a temperature from about 0°C to about 25°C. Upon completion of hydrolysis, the reaction mixture is neutralized, *e.g.*, with dilute HCl, to provide compound **F2**.

Scheme H

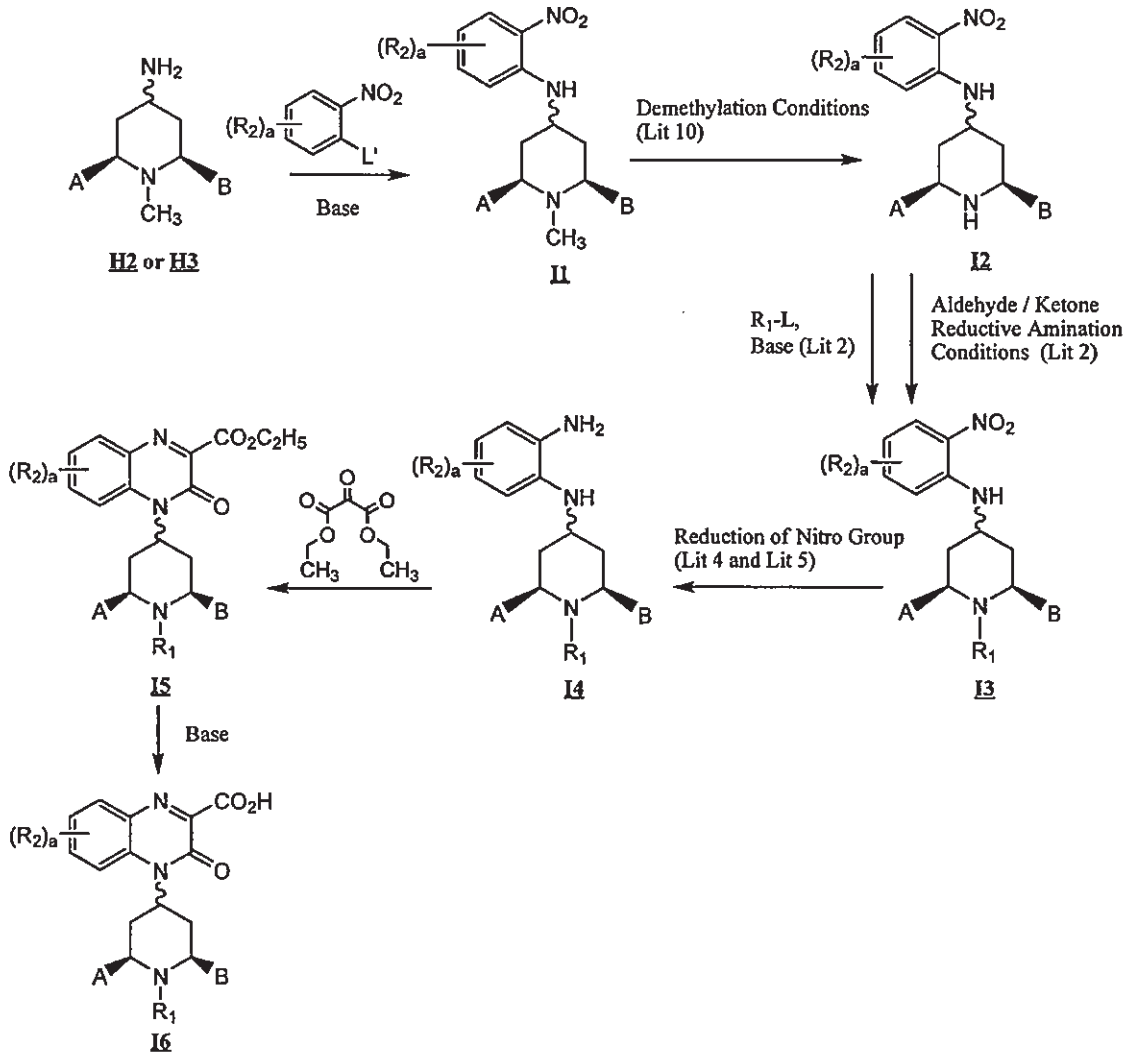


In Scheme H and the other schemes, "Lit 8" refers to "A Modified Palladium Catalyzed Reductive Amination Procedure," M. Allegretti *et al.*, *Tetrahedron Let.*, 58:5669-5674 (2002) and "Lit 9" refers to "Molecular Features Associated with Polyamine Modulation of NMDA Receptors," A.H. Lewin *et al.*, *J. Med. Chem.* 41:988-995 (1998).

The compound of formula **H1**, wherein substituent groups A and B together form a bridge, *e.g.*, a two carbon bridge, is commercially available or can be prepared by methods known to the art.

When substituent groups A and B together form a bridge, *e.g.*, a two carbon bridge, compound **H1** can be converted to compound **H2**, the "*endo*" isomer, under reductive amination conditions using, *e.g.*, ammonium formate and a noble metal catalyst, *e.g.*, palladium on carbon, in a solvent such as EtOH or MeOH as described in reference "Lit 8." Similarly, where substituent groups A and B together form a bridge, *e.g.*, a two carbon bridge, compound **H1** can be reacted with aqueous hydroxylamine in a solvent such as hexanes to form an intermediate hydroxylamine, which can be converted to its oxime by dehydration in a solvent with a high boiling point such as toluene, under Dean-stark conditions. The oxime intermediate can be converted to compound **H3**, the "*exo*" isomer, by reduction using, *e.g.*, sodium in propanol as described in reference "Lit 9."

Scheme I

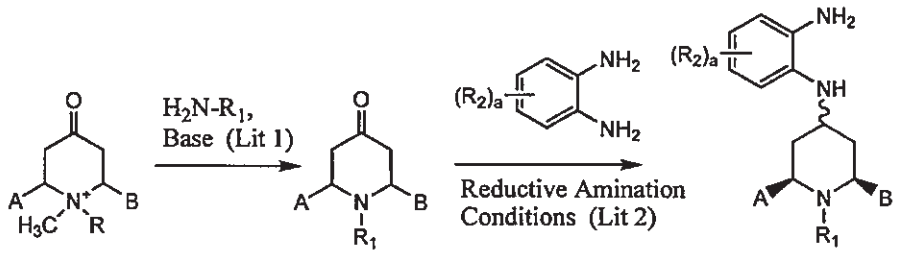


In Scheme I and the other schemes, "Lit 4" refers to the reference P.N. Rylander, *Hydrogenation Methods*, Academic Press, 104-116 (1994), which provides a review of the methods available for the reduction of nitro groups, "Lit 5" refers to the Zinin reduction procedures described in the reference Porter, *Organic Reactions*, 20:455-481 (1973), and "Lit 10" refers to the procedures described by R.A. Olofson *et al.* in *J. Org. Chem.*, 49:2081-2082 (1984) and to R.A. Olofson *et al.* in *Tetrahedron Let.*, 18:1571 (1977).

Substituted-Quinoxaline-Type Bridged-Piperidine Compounds such as **I6** where substituent groups A and B together form a bridge, *e.g.*, a two carbon bridge, can be prepared as described in Scheme I. Compound **H2** (the "*endo*" isomer) or **H3** (the "*exo*" isomer) (where substituent groups A and B together form a bridge, *e.g.*, a two carbon bridge) can be converted to compound **I1** by reaction with a substituted or unsubstituted 2-halo-1-nitrobenzene (where the halo is fluoride or chloride) and a base such as K_2CO_3, in a suitable solvent such as DMF or MeCN at a temperature from about 20°C to about 100°C. Compound **I1** can be demethylated to give compound **I2** using,

e.g., 1-chloromethylchloroformate in a solvent such as 1,2-dichloroethane, followed by treatment with MeOH as described in "Lit 10." Compound **I2** can be converted to compound **I3** (similar to steps described in reference "Lit 2" in Scheme A). Compound **I3** can be converted to compound **I4** by hydrogenation using a catalyst under a hydrogen atmosphere or by chemical means using a reducing agent similar to steps described in "Lit 4" and "Lit 5". Compound **I4** can be converted to compound **I5** by reaction with diethyl 2-oxomalonate in a solvent with a high boiling point such as toluene or xylene under reflux conditions. Compound **I5** can be converted to the carboxylic acid derivative **I6** by hydrolysis using a base such as aqueous NaOH in a suitable solvent such as MeOH or EtOH, followed by neutralization using an acid such as dilute HCl.

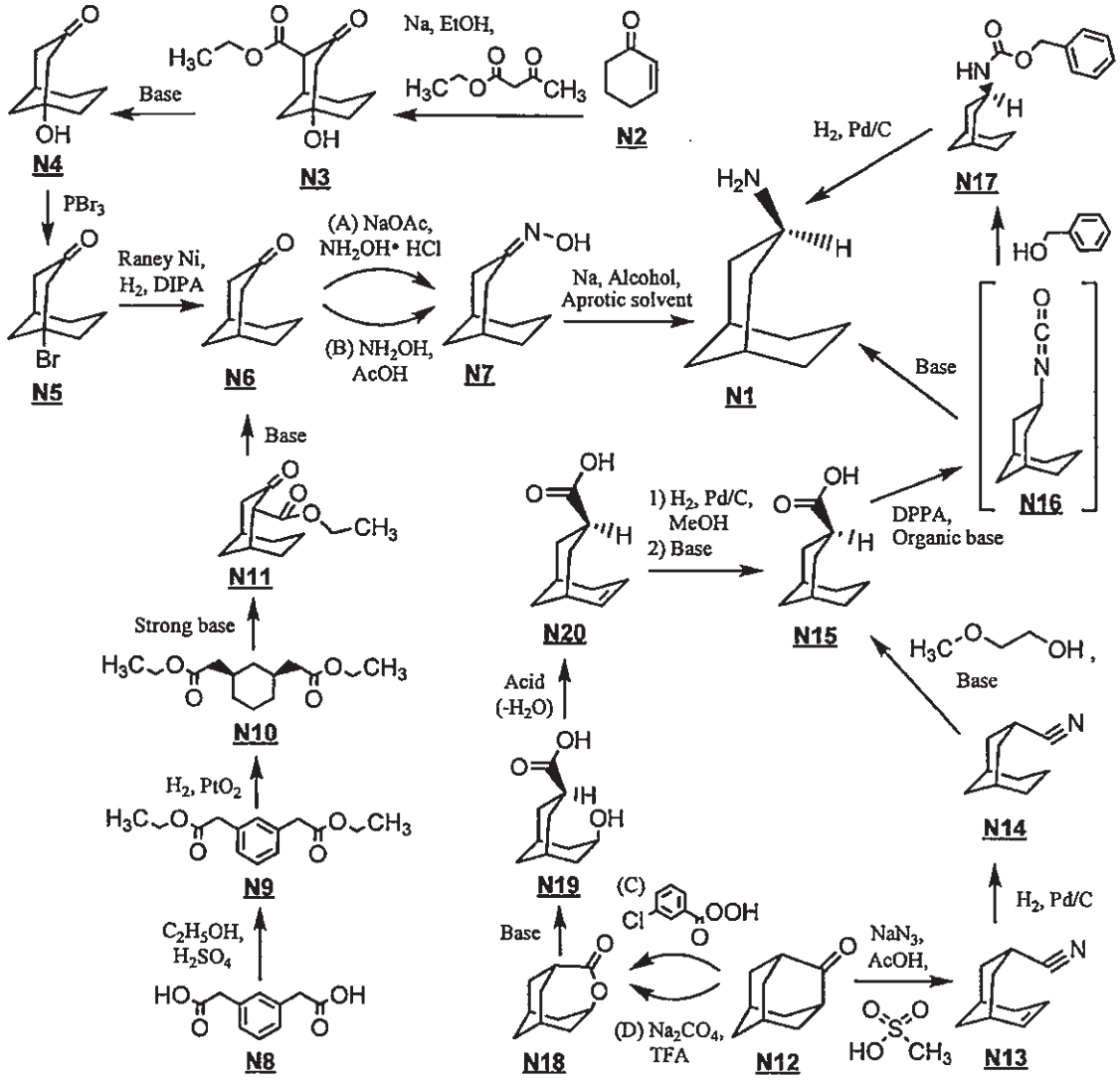
Scheme L



A1 **A3** **I4**

Compound **I4** can be prepared, as shown in Scheme L, from compound **A1** (similar to steps described in Scheme A). Where substituent groups A and B of compound **I4** form a bridge, *e.g.*, a two carbon bridge, the two isomers, "*exo*" and "*endo*," can be separated by chromatography and can be separately converted to compounds such as **F1**, **F2**, and the like as described earlier in Scheme F.

Scheme N



As shown in Scheme N, compound N1, which can comprise an R_1 group, can be prepared by a number of synthetic routes. For example, taking into account the procedures disclosed in "Improved synthetic methods for bicyclo[3.3.1]nonan-3-one," T. Mosose and O. Muraoka, *Chem. Pharmaceut. Bull.* 26(1):288-295 (1978), compound N2 can be reacted with ethyl 3-oxobutanoate and a base, such as sodium ethoxide or potassium *tert*-butoxide which is optionally formed from metallic sodium and the corresponding alcohol, in an alcoholic solvent, such as MeOH or EtOH, under reflux for from about 24h to about 48h to provide compound N3. Compound N3 can be converted to compound N4 using a base, such as NaOH or KOH, in a solvent, such as MeOH or EtOH, and water at a temperature of from about 70°C to about 100°C for from about 4h to about 6h. Compound N4 can be reacted with phosphorus tribromide in a nonpolar solvent, such as DCM, 1,2-dichloroethane or $CHCl_3$, at a temperature of from about 0°C to about 25°C to provide compound N5, which can immediately be treated with Raney nickel and diisopropylamine in a solvent, such as

THF or DME, under an atmosphere of hydrogen to provide compound **N6**.

Thereafter, compound **N6** can be reacted with hydroxylamine or a salt thereof and a base, such as sodium acetate, in a solvent, such as EtOH, to provide compound **N7** (shown as "(A)" in Scheme N). Alternatively, compound **N7** can be prepared from compound **N6** using an aqueous solution of hydroxylamine and a weak acid, such as acetic acid, in a solvent, such as THF, DME or 1,4-dioxane (shown as "(B)" in Scheme N). Compound **N7** can be converted to compound **N1** using an alkali metal, such as sodium or potassium, and an alcohol, such as EtOH or isopropanol, in an inert solvent, such as toluene or xylene, at a temperature of from about 100°C to about 130°C.

If desired, taking into account the procedures provided in H.K. Hall, *J. Org. Chem.* 28:3213-3214 (1963), compound **N6** can be prepared from compound **N8**, 2,2'-(1,3-phenylene)diacetic acid. Compound **N8** can be converted to the diethyl ester using, for example, oxalyl chloride, thionyl chloride or sulfuric acid, in an inert solvent, such as DCM, followed by treatment with EtOH. The ester compound **N9** can be dissolved in a solvent, such as acetic acid, and treated with a catalyst, such as a platinum metal catalyst, *e.g.*, platinum oxide, under from about 1atm to about 10atm hydrogen gas pressure to provide compound **N10** as a mixture of *cis* and *trans* isomers with a preponderance of the *cis* isomer. Compound **N10** can be dissolved in a solvent, such as THF, DME or 1,4-dioxane, and reacted with a strong base, such as sodium hydride or potassium *tert*-butoxide, at a temperature of from about 50°C to about 100°C to provide compound **N11**, which can be converted to compound **N6** using a strong base, such as NaOH or KOH, in a solvent, such as MeOH or EtOH.

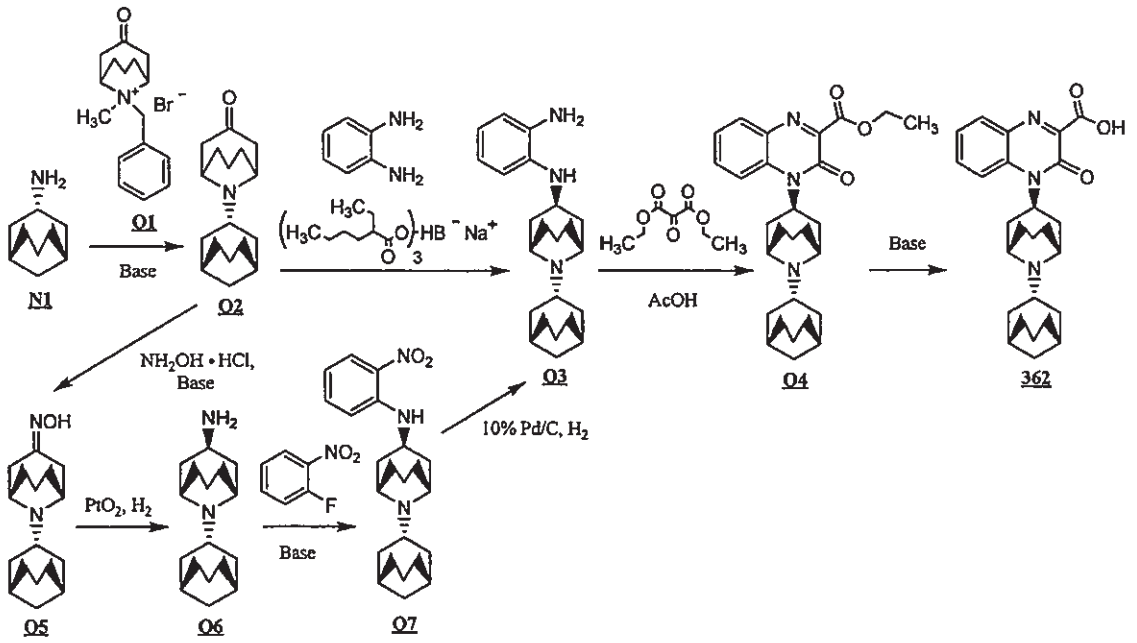
Alternatively, compound **N1** can be prepared from compound **N12**, adamantane-2-one. By one route, compound **N12** can be converted to compound **N15** via compounds **N13** and **N14** by using procedures provided in J.A. Peters, J.M. Van Der Toorn and H. Van Bekkumm, *Tetrahedron* 31:2273-2281 (1975). Compound **N15** can be converted to compound **N17** using the Curtius rearrangement procedure provided in "Diphenylphosphoryl azide a new convenient reagent for a modified Curtius rearrangement and for peptide synthesis," T. Shioiri, K. Ninomiya, S. Yamada, *J. Amer. Chem. Soc.* 94:6202-6205 (1972), whereby compound **N15** is reacted with diphenyl phosphoryl azide and an organic base, such as triethylamine, in an inert solvent, such as benzene or toluene, at a temperature of about 70°C to provide intermediate isocyanate compound **N16** which, upon reaction with benzyl alcohol, provides compound **N17**. Compound **N17** can be converted to compound **N1** by hydrogenolysis using a catalyst, such as a platinum group metal catalyst, *e.g.*, palladium on charcoal, in a solvent such as MeOH or EtOH under a hydrogen atmosphere.

If desired, compound **N1** can be prepared from compound **N15** by synthesizing intermediate isocyanate compound **N16** as described above then reacting it with a base, such as aqueous NaOH or aqueous KOH, in a solvent, such as THF, at a temperature of from about -5°C to

about 0°C to provide compound **N1**, which can be isolated as either its hydrochloride or diphenyl phosphate salt.

If desired, compound **N18** can be prepared from compound **N12** by reaction of compound **N12** with 3-chlorobenzoperoxoic acid in a solvent, such as $CHCl_3$ or DCM, at a temperature of about 25°C (shown as "(C)" in Scheme N). Alternatively, compound **N18** can be prepared from compound **N12** using sodium percarbonate in trifluoroacetic acid as solvent and reagent at a temperature of from about 25°C to about 40°C (shown as "(D)" in Scheme N). Compound **N18** can be converted to compound **N19** by using a base, such as NaOH or KOH, in water and a solvent, such as MeOH, EtOH or 2-methoxyethanol, under reflux for from about 24h to about 48h. Compound **N19** can be converted to compound **N20** by acid catalyzed dehydration using, for example, *p*-toluene sulfonic acid or methane sulfonic acid, in a solvent, such as toluene or xylene. Compound **N20** can be converted to compound **N15** by hydrogenation using a catalyst, such as palladium on charcoal, in MeOH followed by treatment of the product with NaOH or KOH in water.

Scheme O

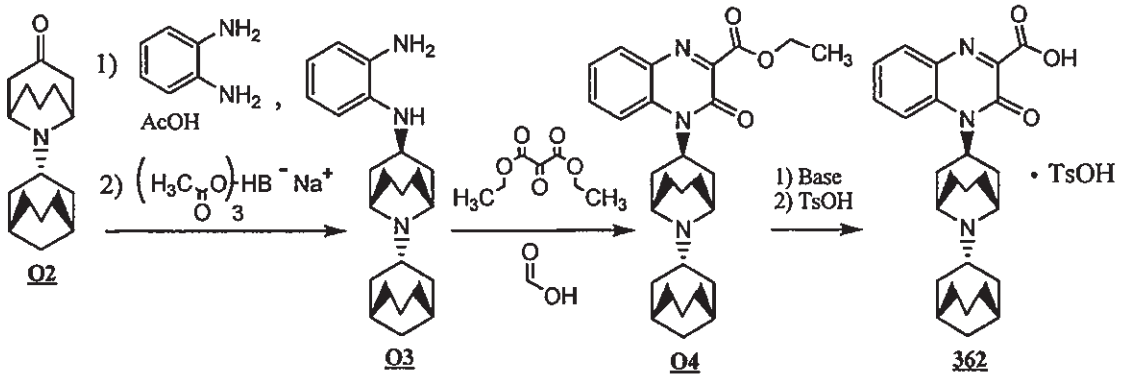


As shown in Scheme O, an exemplary Substituted Quinoxaline-Type Bridged-Piperidine Compound comprising an R_1 group formed from compound **N1** can be prepared by a number of synthetic routes. For purposes of exemplification only, while the product illustrated in Scheme O is Substituted Quinoxaline-Type Bridged-Piperidine Compound **362**, as those in the art will recognize this scheme is of course non-limiting and applicable to the preparation of other Substituted Quinoxaline-Type Bridged-Piperidine Compounds. For example, compound **N1**, its hydrochloride, or its diphenylphosphate salt can be reacted with compound **O1**, pseudopelletierine benzylbromide

salt, in a solvent, such as EtOH and water, and a base, such as K_2CO_3 or Na_2CO_3, at a temperature of from about 25°C to about 100°C to provide compound **O2**. Compound **O2** can be converted to compound **O3** by treatment with excess 1,2-phenylenediamine and a sterically hindered reducing agent, such as sodium tris-(2-ethylhexanoyl)borohydride, in a solvent, such as DCM, at a temperature of from about 25°C to about 40°C. Compound **O3** can be converted to compound **O4** by reaction with diethyl 2-oxomalonate and acetic acid in a solvent, such as toluene or xylene, at a temperature of from about 80°C to about 110°C. Compound **O4** can be converted to the exemplary Substituted Quinoxaline-Type Bridged-Piperidine Compound **362** using a base, such as NaOH or KOH, in water and a solvent, such as MeOH, EtOH or THF.

Alternatively, compound **O3** can be prepared from compound **O2** in a four step procedure as follows. Compound **O2** can be reacted with hydroxylamine hydrochloride in a base, such as an inorganic base, *e.g.*, sodium acetate, or an organic base, *e.g.*, pyridine, in a solvent, such as EtOH, to provide oxime compound **O5**. Compound **O5** can be reduced to the *endo* amine isomer compound **O6** in good stereoselectivity by using a catalyst, such as a platinum group metal catalyst, *e.g.*, platinum oxide or palladium on charcoal, in a solvent, such as acetic acid, under an atmosphere of from about 1atm to about 5atm of hydrogen. Compound **O6** can be converted to compound **O7** by reaction with a 1-halo-2-nitrobenzene, such as 2-fluoro-nitrobenzene or 2-chloro-nitrobenzene, and a base, such as K_2CO_3 or TEA, in a solvent, such as DMF, *N*-methylpyrrolidone, MeCN or 1,4-dioxane, at a temperature of from about 100°C to about 110°C. Compound **O7** can be converted to compound **O3** under hydrogenation conditions using a catalyst, such as Raney nickel, palladium on charcoal or platinum oxide, in a solvent, such as MeOH or EtOH.

Scheme P



Alternatively, as shown in Scheme P an exemplary Substituted Quinoxaline-Type Bridged-Piperidine Compound comprising an R_1 group formed from compound **N1** can be prepared by a method beginning with a two-step, "one-pot" procedure for converting compound **O2** to compound **O3**. For purposes of exemplification only, while the product illustrated in Scheme P is Substituted Quinoxaline-Type Bridged-Piperidine Compound **362**, as those in the art will recognize this

scheme is of course non-limiting and applicable to the preparation of other Substituted Quinoxaline-Type Bridged-Piperidine Compounds. Compound O2 can be reacted with an excess of 1,2-phenylenediamine, from 1.2 to 3.0 equivalents, and acetic acid in a solvent, such as THF or DME (diglyme), and the intermediate imine (comprising a C=N group) can immediately be reacted with a reducing agent, such as sodium triacetoxyborohydride, to provide compound O3. Compound O3 can be converted to compound O4 by reaction with diethyl 2-oxomalonate and formic acid in a solvent, such as toluene or xylene, at a temperature of from about 80°C to about 110°C. Compound O4 can be converted to the exemplary Substituted Quinoxaline-Type Bridged-Piperidine Compound by reaction with a base, such as NaOH or KOH, in water and a co-solvent, such as THF or DME. After the reaction is complete, excess TsOH in THF can be added to provide the tosylate salt of the exemplary Substituted Quinoxaline-Type Bridged-Piperidine Compound 362.

4.6 Therapeutic Uses of the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds

In accordance with the invention, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds are administered to an animal in need of treatment or prevention of a Condition.

In one embodiment, an effective amount of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound can be used to treat or prevent any condition treatable or preventable by inhibiting the activity of the ORL-1 receptor. Examples of Conditions that are treatable or preventable by inhibiting the activity of the ORL-1 receptor include, but are not limited to, pain (CNS effect), memory disorders, obesity, constipation, depression, dementia, and Parkinsonism.

In another embodiment, an effective amount of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound can be used to treat or prevent any condition treatable or preventable by activating the ORL-1 receptor. Examples of Conditions that are treatable or preventable by activating the ORL-1 receptor include, but are not limited to, pain (PNS effect), anxiety, cough, diarrhea, blood pressure disorder (via vasodilation and via diuresis), epilepsy, anorexia/cachexia, urinary incontinence, and drug abuse.

The Substituted-Quinoxaline-Type Bridged-Piperidine Compounds can be used to treat or prevent acute or chronic pain. Examples of pain that can be treated or prevented using a Substituted-Quinoxaline-Type Bridged-Piperidine Compound include, but are not limited to, cancer pain, neuropathic pain, labor pain, myocardial infarction pain, pancreatic pain, colic pain, post-operative pain, headache pain, muscle pain, arthritic pain, and pain associated with a periodontal disease, including gingivitis and periodontitis.

The Substituted-Quinoxaline-Type Bridged-Piperidine Compounds can also be used to treat or prevent pain associated with inflammation or with an inflammatory disease in an animal.

Such pain can arise where there is an inflammation of the body tissue which can be a local inflammatory response or a systemic inflammation. For example, a Substituted-Quinoxaline-Type Bridged-Piperidine Compound can be used to treat or prevent pain associated with inflammatory diseases including, but not limited to, organ transplant rejection; reoxygenation injury resulting from organ transplantation (see Grupp *et al.*, *J. Mol, Cell Cardiol.* 31:297-303 (1999)) including, but not limited to, transplantation of the heart, lung, liver, or kidney; chronic inflammatory diseases of the joints, including arthritis, rheumatoid arthritis, osteoarthritis and bone diseases associated with increased bone resorption; inflammatory bowel diseases, such as ileitis, ulcerative colitis, Barrett's syndrome, and Crohn's disease; inflammatory lung diseases, such as asthma, adult respiratory distress syndrome, and chronic obstructive airway disease; inflammatory diseases of the eye, including corneal dystrophy, trachoma, onchocerciasis, uveitis, sympathetic ophthalmitis and endophthalmitis; chronic inflammatory disease of the gum, including gingivitis and periodontitis; tuberculosis; leprosy; inflammatory diseases of the kidney, including uremic complications, glomerulonephritis and nephrosis; inflammatory disease of the skin, including sclerodermatitis, psoriasis and eczema; inflammatory diseases of the central nervous system, including chronic demyelinating diseases of the nervous system, multiple sclerosis, AIDS-related neurodegeneration and Alzheimer 's disease, infectious meningitis, encephalomyelitis, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis and viral or autoimmune encephalitis; autoimmune diseases, including Type I and Type II diabetes mellitus; diabetic complications, including, but not limited to, diabetic cataract, glaucoma, retinopathy, nephropathy (such as microaluminuria and progressive diabetic nephropathy), gangrene of the feet, atherosclerotic coronary arterial disease, peripheral arterial disease, nonketotic hyperglycemic-hyperosmolar coma, foot ulcers, joint problems, and a skin or mucous membrane complication (such as an infection, a shin spot, a candidal infection or necrobiosis lipoidica diabeticorum), immune-complex vasculitis, and systemic lupus erythematosus (SLE); inflammatory disease of the heart, such as cardiomyopathy, ischemic heart disease hypercholesterolemia, and artherosclerosis; as well as various other diseases that can have significant inflammatory components, including preeclampsia, chronic liver failure, brain and spinal cord trauma, and cancer. A Substituted-Quinoxaline-Type Bridged-Piperidine Compound can also be used to treat or prevent pain associated with inflammatory disease that can, for example, be a systemic inflammation of the body, exemplified by gram-positive or gram negative shock, hemorrhagic or anaphylactic shock, or shock induced by cancer chemotherapy in response to pro-inflammatory cytokines, *e.g.*, shock associated with pro-inflammatory cytokines. Such shock can be induced, *e.g.*, by a chemotherapeutic agent that is administered as a treatment for cancer.

The Substituted-Quinoxaline-Type Bridged-Piperidine Compounds can also be used to treat or prevent pain associated with nerve injury (*i.e.*, neuropathic pain). Chronic neuropathic pain

is a heterogenous disease state with an unclear etiology. In chronic neuropathic pain, the pain can be mediated by multiple mechanisms. This type of pain generally arises from injury to the peripheral or central nervous tissue. The syndromes include pain associated with spinal cord injury, multiple sclerosis, post-herpetic neuralgia, trigeminal neuralgia, phantom pain, causalgia, and reflex sympathetic dystrophy and lower back pain. The chronic pain is different from acute pain in that chronic neuropathic pain patients suffer the abnormal pain sensations that can be described as spontaneous pain, continuous superficial burning and/or deep aching pain. The pain can be evoked by heat-, cold-, and mechano-hyperalgesia, or by heat-, cold-, or mechano-allodynia.

Chronic neuropathic pain can be caused by injury or infection of peripheral sensory nerves. It includes, but is not limited to, pain from peripheral nerve trauma, herpes virus infection, diabetes mellitus, causalgia, plexus avulsion, neuroma, limb amputation, and vasculitis. Neuropathic pain can also be caused by nerve damage from chronic alcoholism, human immunodeficiency virus infection, hypothyroidism, uremia, or vitamin deficiencies. Stroke (spinal or brain) and spinal cord injury can also induce neuropathic pain. Cancer-related neuropathic pain results from tumor growth compression of adjacent nerves, brain, or spinal cord. In addition, cancer treatments, including chemotherapy and radiation therapy, can cause nerve injury. Neuropathic pain includes but is not limited to pain caused by nerve injury such as, for example, the pain from which diabetics suffer.

The Substituted-Quinoxaline-Type Bridged-Piperidine Compounds can be used to treat or prevent a migraine including, but not limited to, migraine without aura ("common migraine"), migraine with aura ("classic migraine"), migraine without headache, basilar migraine, familial hemiplegic migraine, migrainous infarction, and migraine with prolonged aura.

According to the invention, some of the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds are agonists at the ORL-1 receptor, some of the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds are partial agonists at the ORL-1 receptor, and some of the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds are antagonists at the ORL-1 receptor. In another embodiment, a Substituted-Quinoxaline-Type Bridged-Piperidine Compound is an agonist at the ORL-1 receptor and an agonist at a μ, κ and/or δ opioid receptor, particularly at a μ opioid receptor. In another embodiment, a Substituted-Quinoxaline-Type Bridged-Piperidine Compound is a partial agonist at the ORL-1 receptor and an agonist at a μ, κ and/or δ opioid receptor, particularly at a μ opioid receptor. In another embodiment, a Substituted-Quinoxaline-Type Bridged-Piperidine Compound is an antagonist at the ORL-1 receptor and an agonist at a μ, κ and/or δ opioid receptor, particularly at a μ opioid receptor. In another embodiment, a Substituted-Quinoxaline-Type Bridged-Piperidine Compound is an agonist at the ORL-1 receptor and an antagonist at a μ, κ and/or δ opioid receptor, particularly at a μ opioid receptor. In another embodiment, a Substituted-Quinoxaline-Type Bridged-Piperidine Compound is a partial agonist at

the ORL-1 receptor and an antagonist at a μ, κ and/or δ opioid receptor, particularly at a μ opioid receptor. In another embodiment, a Substituted-Quinoxaline-Type Bridged-Piperidine Compound is an antagonist at the ORL-1 receptor and an antagonist at a μ, κ and/or δ opioid receptor, particularly at a μ opioid receptor.

The invention also provides methods for inhibiting ORL-1 receptor function in a cell, comprising contacting a cell capable of expressing the ORL-1 receptor with an amount of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound effective to inhibit ORL-1 receptor function in the cell. This method can be adapted for use *in vitro* as part of an assay to select compounds that can be useful for treating or preventing a Condition in an animal. Alternatively, this method can be adapted for use *in vivo*, (*i.e.*, in an animal such as a human) by contacting a cell in the animal with an effective amount of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound. In one embodiment, the method is useful for treating or preventing pain in an animal in need of such treatment or prevention. In another embodiment, the method is useful for treating or preventing a memory disorder, obesity, constipation, depression, dementia, or Parkinsonism in an animal in need of such treatment or prevention.

The invention also relates to methods for activating ORL-1 receptor function in a cell, comprising contacting a cell capable of expressing the ORL-1 receptor with an amount of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound effective to activate ORL-1 receptor function in the cell. This method can be adapted for use *in vitro* as part of an assay to select compounds useful for treating or preventing, pain, anxiety, cough, diarrhea, high blood pressure, epilepsy, anorexia/cachexia, urinary incontinence, or drug abuse. Alternatively, the method can be adapted for use *in vivo* (*i.e.*, in an animal such as a human), by contacting a cell in the animal with an effective amount of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound. In one embodiment the method is useful for treating or preventing pain in an animal in need of such treatment or prevention. In another embodiment, the method is useful for treating or preventing anxiety, cough, diarrhea, high blood pressure, epilepsy, anorexia/chachexia, urinary incontinence, or drug abuse in an animal in need of such treatment or prevention.

Examples of tissue comprising cells capable of expressing the ORL-1 receptor include but are not limited to brain, spinal cord, vas deferens, and gastrointestinal tract tissue. Methods for assaying cells that express the ORL-1 receptor are known in the art; for example, see Y. Shimohigashi *et al.*, "Sensitivity of opioid receptor-like receptor ORL1 for chemical modification on nociceptin, a naturally occurring nociceptive peptide," *J. Biol. Chem.* 271(39):23642-23645 (1996); M. Narita *et al.*, "Identification of the G-protein coupled ORL1 receptor in the mouse spinal cord by [^{35}S]-GTPγS binding and immunohistochemistry," *Brit. J. Pharmacol.* 128:1300-1306 (1999); G. Milligan, "Principles: Extending then utility of [^{35}S]GTPγS binding assays," *TIPS*

14:110-112 (2003): and S. Lazareno, "Measurement of agonist-stimulated [^{35}S]GTPγS binding to cell membranes," *Methods in Molecular Biology* Vol. 106:231245 (1999).

4.7 Therapeutic/Prophylactic Administration and Compositions of the Invention

Due to their activity, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds are advantageously useful in human and veterinary medicine. As described above, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds are useful for treating or preventing a Condition in an animal in need thereof. The Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention can be administered to any animal requiring modulation of the opioid and/or ORL-1 receptors.

When administered to an animal, a Substituted-Quinoxaline-Type Bridged-Piperidine Compound can be administered as a component of a composition that comprises a pharmaceutically acceptable carrier or excipient. The invention compositions, which comprise a Substituted-Quinoxaline-Type Bridged-Piperidine Compound, can be administered orally. A Substituted-Quinoxaline-Type Bridged-Piperidine Compound can also be administered by any other convenient route, for example, by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral, rectal, and intestinal mucosa, etc.) and can be administered together with a second therapeutically active agent. Administration can be systemic or local. Various delivery systems are known, *e.g.*, encapsulation in liposomes, microparticles, microcapsules, multiparticulates, capsules, etc., and can be used to administer a Substituted-Quinoxaline-Type Bridged-Piperidine Compound.

Methods of administration include, but are not limited to, intradermal, intramuscular, intraperitoneal, parenteral, intravenous, subcutaneous, intranasal, epidural, oral, sublingual, intracerebral, intravaginal, transdermal, rectal, by inhalation, or topical, particularly to the ears, nose, eyes, or skin. The method of administration is left to the discretion of the practitioner. In most instances, administration will result in the release of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound into the bloodstream.

In specific embodiments, it can be desirable to administer a Substituted-Quinoxaline-Type Bridged-Piperidine Compound locally. This can be achieved, for example and not by way of limitation, by local infusion during surgery, topical application, *e.g.*, in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository or enema, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers.

In certain embodiments, it can be desirable to introduce a Substituted-Quinoxaline-Type Bridged-Piperidine Compound into the central nervous system or gastrointestinal tract by any

suitable route, including intraventricular, intrathecal, and epidural injection, and enema. Intraventricular injection can be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir.

Pulmonary administration can also be employed, *e.g.*, by use of an inhaler or nebulizer, and formulation with an aerosolizing agent, or via perfusion in a fluorocarbon or synthetic pulmonary surfactant. In certain embodiments, a Substituted-Quinoxaline-Type Bridged-Piperidine Compound can be formulated as a suppository, with traditional binders and excipients such as triglycerides.

When a Substituted-Quinoxaline-Type Bridged-Piperidine Compound of the invention is incorporated for parenteral administration by injection (*e.g.*, continuous infusion or bolus injection), the formulation for parenteral administration can be in the form of a suspension, solution, emulsion in an oily or aqueous vehicle, and such formulations can further comprise pharmaceutically necessary additives such as one or more stabilizing agents, suspending agents, dispersing agents, and the like. A Substituted-Quinoxaline-Type Bridged-Piperidine Compound of the invention can also be in the form of a powder for reconstitution as an injectable formulation.

In another embodiment, a Substituted-Quinoxaline-Type Bridged-Piperidine Compound can be delivered in a vesicle, in particular a liposome (*see* Langer, *Science* 249:1527-1533 (1990); and Treat *et al.*, *Liposomes in the Therapy of Infectious Disease and Cancer* 317-327 and 353-365 (1989)).

In yet another embodiment, a Substituted-Quinoxaline-Type Bridged-Piperidine Compound can be delivered in a controlled-release system or sustained-release system (*see*, *e.g.*, Goodson, "Dental Applications" (pp. 115-138) in *Medical Applications of Controlled Release, Vol. 2, Applications and Evaluation*, R.S. Langer and D.L. Wise eds., CRC Press (1984)). Other controlled- or sustained-release systems discussed in the review by Langer, *Science* 249:1527-1533 (1990) can be used. In one embodiment, a pump can be used (Langer, *Science* 249:1527-1533 (1990); Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201 (1987); Buchwald *et al.*, *Surgery* 88:507 (1980); and Saudek *et al.*, *N. Engl. J. Med.* 321:574 (1989)). In another embodiment, polymeric materials can be used (*see Medical Applications of Controlled Release* (Langer and Wise eds., 1974); *Controlled Drug Bioavailability, Drug Product Design and Performance* (Smolen and Ball eds., 1984); Ranger and Peppas, *J. Macromol. Sci. Rev. Macromol. Chem.* 23:61 (1983); Levy *et al.*, *Science* 228:190 (1985); During *et al.*, *Ann. Neurol.* 25:351 (1989); and Howard *et al.*, *J. Neurosurg.* 71:105 (1989)). In yet another embodiment, a controlled- or sustained-release system can be placed in proximity of a target of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound, *e.g.*, the spinal column, brain, or gastrointestinal tract, thus requiring only a fraction of the systemic dose.

The invention compositions can optionally comprise a suitable amount of a pharmaceutically acceptable excipient so as to provide the form for proper administration to the animal. Such a pharmaceutical excipient can be a diluent, suspending agent, solubilizer, binder, disintegrant, preservative, coloring agent, lubricant, and the like. The pharmaceutical excipient can be a liquid, such as water or an oil, including those of petroleum, animal, vegetable, or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil, and the like. The pharmaceutical excipient can be saline, gum acacia, gelatin, starch paste, talc, keratin, colloidal silica, urea, and the like. In addition, auxiliary, stabilizing, thickening, lubricating, and coloring agents can be used. In one embodiment, the pharmaceutically acceptable excipient is sterile when administered to an animal. Water is a particularly useful excipient when a Substituted-Quinoxaline-Type Bridged-Piperidine Compound is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid excipients, particularly for injectable solutions. Suitable pharmaceutical excipients also include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene glycol, water, ethanol, and the like. The invention compositions, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. Specific examples of pharmaceutically acceptable carriers and excipients that can be used to formulate oral dosage forms are described in the *Handbook of Pharmaceutical Excipients*, American Pharmaceutical Association (1986).

The invention compositions can take the form of solutions, suspensions, emulsions, tablets, pills, pellets, capsules, capsules containing liquids, powders, sustained-release formulations, suppositories, emulsions, aerosols, sprays, suspensions, or any other form suitable for use. In one embodiment, the composition is in the form of a capsule (*see, e.g.*, U.S. Patent No. 5,698,155). Other examples of suitable pharmaceutical excipients are described in *Remington's Pharmaceutical Sciences* 1447-1676 (Alfonso R. Gennaro ed., 19th ed. 1995), incorporated herein by reference.

In one embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds are formulated in accordance with routine procedures as a composition adapted for oral administration to human beings. A Substituted-Quinoxaline-Type Bridged-Piperidine Compound to be orally delivered can be in the form of tablets, capsules, gelcaps, caplets, lozenges, aqueous or oily solutions, suspensions, granules, powders, emulsions, syrups, or elixirs, for example. When a Substituted-Quinoxaline-Type Bridged-Piperidine Compound is incorporated into oral tablets, such tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, multiply compressed or multiply layered. Techniques and compositions for making solid oral dosage forms are described in *Pharmaceutical Dosage Forms: Tablets* (Lieberman, Lachman and Schwartz, eds., 2nd ed.) published by Marcel Dekker, Inc. Techniques and compositions for making tablets (compressed and molded), capsules (hard and soft gelatin) and pills are also described in

Remington's Pharmaceutical Sciences 1553-1593 (Arthur Osol, ed., 16th ed., Mack Publishing, Easton, PA 1980).

Liquid oral dosage forms include aqueous and nonaqueous solutions, emulsions, suspensions, and solutions and/or suspensions reconstituted from non-effervescent granules, optionally containing one or more suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, coloring agents, flavoring agents, and the like. Techniques and composition for making liquid oral dosage forms are described in *Pharmaceutical Dosage Forms: Disperse Systems*, (Lieberman, Rieger and Banker, eds.) published by Marcel Dekker, Inc.

When a Substituted-Quinoxaline-Type Bridged-Piperidine Compound is to be injected parenterally, it can be, *e.g.*, in the form of an isotonic sterile solution. Alternatively, when a Substituted-Quinoxaline-Type Bridged-Piperidine Compound is to be inhaled, it can be formulated into a dry aerosol or can be formulated into an aqueous or partially aqueous solution.

An orally administered Substituted-Quinoxaline-Type Bridged-Piperidine Compound can contain one or more agents, for example, sweetening agents such as fructose, aspartame or saccharin; flavoring agents such as peppermint, oil of wintergreen, or cherry; coloring agents; and preserving agents, to provide a pharmaceutically palatable preparation. Moreover, where in tablet or pill form, the compositions can be coated to delay disintegration and absorption in the gastrointestinal tract thereby providing a sustained action over an extended period of time. Selectively permeable membranes surrounding an osmotically active driving compound are also suitable for orally administered compositions. In these latter platforms, fluid from the environment surrounding the capsule is imbibed by the driving compound, which swells to displace the agent or agent composition through an aperture. These delivery platforms can provide an essentially zero order delivery profile as opposed to the spiked profiles of immediate release formulations. A time-delay material such as glycerol monostearate or glycerol stearate can also be used. Oral compositions can include standard excipients such as mannitol, lactose, starch, magnesium stearate, sodium saccharin, cellulose, and magnesium carbonate. In one embodiment, the excipients are of pharmaceutical grade.

In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds can be formulated for intravenous administration. Typically, compositions for intravenous administration comprise sterile isotonic aqueous buffer. Where necessary, the compositions can also include a solubilizing agent. A Substituted-Quinoxaline-Type Bridged-Piperidine Compound for intravenous administration can optionally include a local anesthetic such as benzocaine or prilocaine to lessen pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampule or sachette indicating the

quantity of active agent. Where a Substituted-Quinoxaline-Type Bridged-Piperidine Compound is to be administered by infusion, it can be dispensed, for example, with an infusion bottle containing sterile pharmaceutical grade water or saline. Where a Substituted-Quinoxaline-Type Bridged-Piperidine Compound is administered by injection, an ampule of sterile water for injection or saline can be provided so that the ingredients can be mixed prior to administration.

A Substituted-Quinoxaline-Type Bridged-Piperidine Compound can be administered by controlled-release or sustained-release means or by delivery devices that are known to those in the art. Examples include, but are not limited to, those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; and 5,733,566, each of which is incorporated herein by reference. Such dosage forms can be used to provide controlled- or sustained-release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, multiparticulates, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled- or sustained-release formulations known to those in the art, including those described herein, can be readily selected for use with the active ingredients of the invention. The invention thus encompasses single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled- or sustained-release.

Controlled- or sustained-release pharmaceutical compositions can have a common goal of improving drug therapy over that achieved by their non-controlled or non-sustained-release counterparts. In one embodiment, a controlled- or sustained-release composition comprises a minimal amount of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound to treat or prevent the Condition or a symptom thereof in a minimum amount of time. Advantages of controlled- or sustained-release compositions include extended activity of the drug, reduced dosage frequency, and increased compliance. In addition, controlled- or sustained-release compositions can favorably affect the time of onset of action or other characteristics, such as blood levels of the Substituted-Quinoxaline-Type Bridged-Piperidine Compound, and can thus reduce the occurrence of adverse side effects.

Controlled- or sustained-release compositions can initially release an amount of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound that promptly produces the desired therapeutic or prophylactic effect, and gradually and continually release other amounts of the Substituted-Quinoxaline-Type Bridged-Piperidine Compound to maintain this level of therapeutic or prophylactic effect over an extended period of time. To maintain a constant level of the Substituted-Quinoxaline-Type Bridged-Piperidine Compound in the body, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound can be released from the dosage form at a rate

that will replace the amount of Substituted-Quinoxaline-Type Bridged-Piperidine Compound being metabolized and excreted from the body. Controlled- or sustained-release of an active ingredient can be stimulated by various conditions, including but not limited to, changes in pH, changes in temperature, concentration or availability of enzymes, concentration or availability of water, or other physiological conditions or compounds.

The amount of the Substituted-Quinoxaline-Type Bridged-Piperidine Compound that is effective for the treatment or prevention of a Condition can be determined by standard clinical techniques. In addition, *in vitro* and/or *in vivo* assays can optionally be employed to help identify optimal dosage ranges. The precise dose to be employed will also depend on, *e.g.*, the route of administration and the seriousness of the Condition, and can be decided according to the judgment of a practitioner and/or each animal's circumstances. In other examples thereof, variations will necessarily occur depending upon the weight and physical condition (*e.g.*, hepatic and renal function) of the animal being treated, the affliction to be treated, the severity of the symptoms, the frequency of the dosage interval, the presence of any deleterious side-effects, and the particular compound utilized, among other things.

Suitable effective dosage amounts, however, range from about 0.01mg/kg of body weight to about 3000mg/kg of body weight of the animal per day, although they are typically from about 0.01mg/kg of body weight to about 2500mg/kg of body weight of the animal per day or from about 0.01mg/kg of body weight to about 1000mg/kg of body weight of the animal per day. In one embodiment, the effective dosage amount is about 100mg/kg of body weight of the animal per day or less. In another embodiment, the effective dosage amount ranges from about 0.01mg/kg of body weight to about 100mg/kg of body weight of the animal per day of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound, in another embodiment, about 0.02mg/kg of body weight to about 50mg/kg of body weight of the animal per day, and in another embodiment, about 0.025mg/kg of body weight to about 20mg/kg of body weight of the animal per day.

Administration can be as a single dose or as a divided dose. In one embodiment, an effective dosage amount is administered about every 24hr until the Condition is abated. In another embodiment, an effective dosage amount is administered about every 12hr until the Condition is abated. In another embodiment, an effective dosage amount is administered about every 8hr until the Condition is abated. In another embodiment, an effective dosage amount is administered about every 6hr until the Condition is abated. In another embodiment, an effective dosage amount is administered about every 4hr until the Condition is abated. The effective dosage amounts described herein refer to total amounts administered; that is, if more than one Substituted-Quinoxaline-Type Bridged-Piperidine Compound is administered, the effective dosage amounts correspond to the total amount administered.

Where a cell capable of expressing the ORL-1 receptor, the μ-opioid receptor, the κ-opioid receptor and/or the δ-opioid receptor is contacted with a Substituted-Quinoxaline-Type Bridged-Piperidine Compound *in vitro*, the amount effective for inhibiting or activating that receptor function in a cell will typically range from about 10^{-12} mol/L to about 10^{-4} mol/L, in one embodiment, from about 10^{-12} mol/L to about 10^{-5} mol/L, in another embodiment, from about 10^{-12} mol/L to about 10^{-6} mol/L, and in another embodiment, from about 10^{-12} mol/L to about 10^{-9} mol/L of a solution or suspension of a pharmaceutically acceptable carrier or excipient. In one embodiment, the volume of solution or suspension comprising the Substituted-Quinoxaline-Type Bridged-Piperidine Compound will be from about 0.01μL to about 1mL. In another embodiment, the volume of solution or suspension will be about 200μL.

The Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a binding affinity (K_i) for the human ORL-1 receptor of about 1000nM or less in one embodiment, or about 500nM or less in another embodiment, about 100nM or less in another embodiment, about 50nM or less in another embodiment, or about 20nM or less in another embodiment, or about 5nM or less in another embodiment. The binding affinity K_i can be measured in ways known to the art, *e.g.*, by an assay utilizing membranes from recombinant HEK-293 cells expressing the ORL-1 receptor.

Typically, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 300 or less for binding to ORL-1 receptors. In one embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a Ki (nM) of about 100 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a Ki (nM) of about 35 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a Ki (nM) of about 20 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a Ki (nM) of about 15 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a Ki (nM) of about 10 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a Ki (nM) of about 4 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a Ki (nM) of about 1 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a Ki (nM) of about 0.4 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a Ki (nM) of about 0.1 or less.

ORL-1 GTP EC_{50} is the concentration of a compound providing 50% of the maximal response for the compound at an ORL-1 receptor. Substituted-Quinoxaline-Type Bridged-Piperidine Compounds typically will have an ORL-1 GTP EC_{50} (nM) of about 5000 or less to stimulate ORL-1 receptor function. In one embodiment, the Substituted-Quinoxaline-Type

Bridged-Piperidine Compounds of the invention will have an ORL-1 GTP EC_{50} (nM) of about 1000 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have an ORL-1 GTP EC_{50} (nM) of about 100 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have an ORL-1 GTP EC_{50} (nM) of about 80 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have an ORL-1 GTP EC_{50} (nM) of about 50 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have an ORL-1 GTP EC_{50} (nM) of about 35 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have an ORL-1 GTP EC_{50} (nM) of about 15 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have an ORL-1 GTP EC_{50} (nM) of about 10 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have an ORL-1 GTP EC_{50} (nM) of about 4 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have an ORL-1 GTP EC_{50} (nM) of about 1 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have an ORL-1 GTP EC_{50} (nM) of about 0.4 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have an ORL-1 GTP EC_{50} (nM) of about 0.1 or less.

ORL-1 GTP Emax (%) is the maximal effect elicited by a compound relative to the effect elicited by nociceptin, a standard ORL-1 agonist. Typically, a Substituted-Quinoxaline-Type Bridged-Piperidine Compound of the invention acting as an agonist will have an ORL-1 GTP Emax (%) of about 50% or greater. In one embodiment, agonist Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have an ORL-1 GTP Emax (%) of about 75% or greater. In another embodiment, agonist Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have an ORL-1 GTP Emax (%) of about 85% or greater. In another embodiment, agonist Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have an ORL-1 GTP Emax (%) of about 95% or greater. In another embodiment, agonist Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have an ORL-1 GTP Emax (%) of about 100% or greater. Typically, a Substituted-Quinoxaline-Type Bridged-Piperidine Compound of the invention acting as a partial agonist will have an ORL-1 GTP Emax (%) of less than about 10%. In one embodiment, partial agonist Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have an ORL-1 GTP Emax (%) of less than about 20%. In another embodiment, partial agonist Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have an ORL-1 GTP Emax (%) of less than about 30%. In another embodiment, partial agonist Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have an ORL-1 GTP Emax (%) of less than about 40%. In another

embodiment, partial agonist Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have an ORL-1 GTP Emax (%) of less than about 50%.

The Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a binding affinity (Ki) for the human μ-opioid receptors of about 3000nM or less in one embodiment, or about 1000nM or less in another embodiment, or about 525nM or less in another embodiment, or about 100nM or less in another embodiment, or about 50nM or less in another embodiment, or about 20nM or less in another embodiment, or about 5nM or less in another embodiment.

Typically, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 3000 or less for binding to μ-opioid receptors. In one embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a Ki (nM) of about 1000 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a Ki (nM) of about 650 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a Ki (nM) of about 525 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a Ki (nM) of about 250 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a Ki (nM) of about 100 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a Ki (nM) of about 10 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a Ki (nM) of about 1 or less.

μ GTP EC_{50} is the concentration of a compound providing 50% of the maximal response for the compound at a μ-opioid receptor. Substituted-Quinoxaline-Type Bridged-Piperidine Compounds typically will have a μ GTP EC_{50} (nM) of about 5000 or less to stimulate μ-opioid receptor function. In one embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a μ GTP EC_{50} (nM) of about 4100 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a μ GTP EC_{50} (nM) of about 3100 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a μ GTP EC_{50} (nM) of about 2000 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a μ GTP EC_{50} (nM) of about 1000 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a μ GTP EC_{50} (nM) of about 100 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a μ GTP EC_{50} (nM) of about 10 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a μ GTP EC_{50} (nM) of about 1 or less. In another embodiment, the

Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a μ GTP EC_{50} (nM) of about 0.4 or less.

μ GTP Emax (%) is the maximal effect elicited by a compound relative to the effect elicited by DAMGO, a standard μ agonist. Typically, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a μ GTP Emax (%) of about 10% or greater. In one embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a μ GTP Emax (%) of about 20% or greater. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a μ GTP Emax (%) of about 50% or greater. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a μ GTP Emax (%) of about 65% or greater. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a μ GTP Emax (%) of about 75% or greater. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a μ GTP Emax (%) of about 88% or greater.

Typically, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 20,000 or less for κ receptors. In one embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have substantially no activity. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 10,000 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 5000 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 1000 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 500 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 300 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 100 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 50 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 20 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 15 or less.

κ GTP EC_{50} is the concentration of a compound providing 50% of the maximal response for the compound at a κ receptor. Substituted-Quinoxaline-Type Bridged-Piperidine Compounds typically will have a κ GTP EC_{50} (nM) of about 20,000 or less to stimulate κ opioid receptor function. In one embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 10,000 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 5000 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds

will have a κ GTP EC_{50} (nM) of about 2000 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 1500 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 800 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 500 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 300 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 100 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 50 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 25 or less.

κ GTP Emax (%) is the maximal effect elicited by a compound relative to the effect elicited by U69,593. Typically, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a κ GTP Emax (%) of about 10% or greater. In one embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a κ GTP Emax (%) of about 15% or greater. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a κ GTP Emax (%) of about 30% or greater. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a κ GTP Emax (%) of about 40% or greater. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a κ GTP Emax (%) of about 45% or greater. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a κ GTP Emax (%) of about 75% or greater. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a κ GTP Emax (%) of about 90% or greater.

Typically, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 20,000 or less for δ receptors. In one embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have substantially no activity. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 10,000 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 9000 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 7500 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 6500 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 5000 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 3000 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds

will have a Ki (nM) of about 2500 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 1000 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 500 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 350 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 250 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 100 or less.

δ GTP EC_{50} is the concentration of a compound providing 50% of the maximal response for the compound at a δ receptor. Substituted-Quinoxaline-Type Bridged-Piperidine Compounds typically will have a δ GTP EC_{50} (nM) of about 20,000 or less to stimulate δ opioid receptor function. In one embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a δ GTP EC_{50} (nM) of about 10,000 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a δ GTP EC_{50} (nM) of about 1000 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a δ GTP EC_{50} (nM) of about 100 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a δ GTP EC_{50} (nM) of about 90 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a δ GTP EC_{50} (nM) of about 50 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a δ GTP EC_{50} (nM) of about 25 or less.

δ GTP Emax (%) is the maximal effect elicited by a compound relative to the effect elicited by met-enkephalin. Typically, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a δ GTP Emax (%) of about 10% or greater. In one embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a δ GTP Emax (%) of about 30% or greater. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a δ GTP Emax (%) of about 50% or greater. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a δ GTP Emax (%) of about 75% or greater. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a δ GTP Emax (%) of about 90% or greater. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a δ GTP Emax (%) of about 100% or greater.

The Substituted-Quinoxaline-Type Bridged-Piperidine Compounds can be assayed *in vitro* or *in vivo* for the desired therapeutic or prophylactic activity prior to use in humans. Animal model systems can be used to demonstrate safety and efficacy.

The methods for treating or preventing a Condition in an animal in need thereof can further comprise co-administering to the animal being administered a Substituted-Quinoxaline-Type Bridged-Piperidine Compound (*i.e.*, a first therapeutic agent) a second therapeutic agent. In one embodiment, the second therapeutic agent is administered in an effective amount.

An effective amount of the second therapeutic agent will be known to those skilled the art depending on the agent. However, it is well within the skilled artisan's purview to determine the second therapeutic agent's optimal effective-amount range. In one embodiment of the invention, where a second therapeutic agent is administered to an animal for treatment of a Condition (*e.g.*, pain), the minimal effective amount of the Substituted-Quinoxaline-Type Bridged-Piperidine Compound will be less than its minimal effective amount would be where the second therapeutic agent is not administered. In this embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound and the second therapeutic agent can act synergistically to treat or prevent a Condition.

The second therapeutic agent can be, but is not limited to, an opioid agonist, a non-opioid analgesic, a non-steroidal anti-inflammatory agent, an antimigraine agent, a Cox-II inhibitor, a 5-lipoxygenase inhibitor, an anti-emetic, a β-adrenergic blocker, an anticonvulsant, an antidepressant, a Ca^{2+}-channel blocker, an anti-cancer agent, an agent for treating or preventing UI, an agent for treating or preventing anxiety, an agent for treating or preventing a memory disorder, an agent for treating or preventing obesity, an agent for treating or preventing constipation, an agent for treating or preventing cough, an agent for treating or preventing diarrhea, an agent for treating or preventing high blood pressure, an agent for treating or preventing epilepsy, an agent for treating or preventing anorexia/cachexia, an agent for treating or preventing drug abuse, an agent for treating or preventing an ulcer, an agent for treating or preventing IBD, an agent for treating or preventing IBS, an agent for treating or preventing addictive disorder, an agent for treating or preventing Parkinson's disease and parkinsonism, an agent for treating or preventing a stroke, an agent for treating or preventing a seizure, an agent for treating or preventing a pruritic condition, an agent for treating or preventing psychosis, an agent for treating or preventing Huntington's chorea, an agent for treating or preventing ALS, an agent for treating or preventing a cognitive disorder, an agent for treating or preventing a migraine, an agent for inhibiting vomiting, an agent for treating or preventing dyskinesia, an agent for treating or preventing depression, or any mixture thereof.

Examples of useful opioid agonists include, but are not limited to, alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone,

levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, proheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tilidine, tramadol, pharmaceutically acceptable derivatives thereof, or any mixture thereof.

In certain embodiments, the opioid agonist is selected from codeine, hydromorphone, hydrocodone, oxycodone, dihydrocodeine, dihydromorphine, morphine, tramadol, oxymorphone, pharmaceutically acceptable derivatives thereof, or any mixture thereof.

Examples of useful non-opioid analgesics include, but are not limited to, non-steroidal anti-inflammatory agents, such as aspirin, ibuprofen, diclofenac, naproxen, benoxaprofen, flurbiprofen, fenoprofen, flubufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaprozin, pramoprofen, muroprofen, trioxaprofen, suprofen, aminoprofen, tiaprofenic acid, fluprofen, bucloxic acid, indomethacin, sulindac, tolmetin, zomepirac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac, oxpinac, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid, tolfenamic acid, diflurisal, flufenisal, piroxicam, sudoxicam, isoxicam, a pharmaceutically acceptable derivative thereof, or any mixture thereof. Other suitable non-opioid analgesics include the following, non-limiting, chemical classes of analgesic, antipyretic, nonsteroidal anti-inflammatory drugs: salicylic acid derivatives, including aspirin, sodium salicylate, choline magnesium trisalicylate, salsalate, diflunisal, salicylsalicylic acid, sulfasalazine, and olsalazin; para-aminophenol derivatives including acetaminophen and phenacetin; indole and indene acetic acids, including indomethacin, sulindac, and etodolac; heteroaryl acetic acids, including tolmetin, diclofenac, and ketorolac; anthranilic acids (fenamates), including mefenamic acid and meclofenamic acid; enolic acids, including oxicams (piroxicam, tenoxicam), and pyrazolidinediones (phenylbutazone, oxyphenthartazone); alkanones, including nabumetone; a pharmaceutically acceptable derivative thereof; or any mixture thereof. For a more detailed description of the NSAIDs, *see* Paul A. Insel, *Analgesic-Antipyretic and Anti-inflammatory Agents and Drugs Employed in the Treatment of Gout*, in *Goodman & Gilman's The Pharmacological Basis of Therapeutics* 617-57 (P.B. Molinhoff and R.W. Ruddon eds., 9th ed 1996), and G.R. Hanson, *Analgesic, Antipyretic and Anti-Inflammatory Drugs in Remington: The Science and Practice of Pharmacy Vol II* 1196-1221 (A.R. Gennaro ed. 19th ed. 1995), which are hereby incorporated by reference in their entireties.

Examples of useful Cox-II inhibitors and 5-lipoxygenase inhibitors, as well as combinations thereof, are described in U.S. Patent No. 6,136,839, which is hereby incorporated by reference in its entirety. Examples of useful Cox-II inhibitors include, but are not limited to, celecoxib, DUP-697, flosulide, meloxicam, 6-MNA, L-745337, rofecoxib, nabumetone,

nimesulide, NS-398, SC-5766, T-614, L-768277, GR-253035, JTE-522, RS-57067-000, SC-58125, SC-078, PD-138387, NS-398, flosulide, D-1367, SC-5766, PD-164387, etoricoxib, valdecoxib, parecoxib, a pharmaceutically acceptable derivative thereof, or any mixture thereof.

Examples of useful antimigraine agents include, but are not limited to, alpiropride, bromocriptine, dihydroergotamine, dolasetron, ergocornine, ergocorninine, ergocryptine, ergonovine, ergot, ergotamine, flumedroxone acetate, fonazine, ketanserin, lisuride, lomerizine, methylergonovine, methysergide, metoprolol, naratriptan, oxetorone, pizotyline, propranolol, risperidone, rizatriptan, sumatriptan, timolol, trazodone, zolmitriptan, a pharmaceutically acceptable derivative thereof, or any mixture thereof.

Examples of useful anticonvulsants include, but are not limited to, acetylpheneturide, albutoin, aloxidone, aminoglutethimide, 4-amino-3-hydroxybutyric acid, atrolactamide, beclamide, buramate, calcium bromide, carbamazepine, cinromide, clomethiazole, clonazepam, decimemide, diethadione, dimethadione, doxenitroin, eterobarb, ethadione, ethosuximide, ethotoin, felbamate, fluoresone, gabapentin, 5-hydroxytryptophan, lamotrigine, magnesium bromide, magnesium sulfate, mephenytoin, mephobarbital, metharbital, methetoin, methsuximide, 5-methyl-5-(3-phenanthryl)-hydantoin, 3-methyl-5-phenylhydantoin, narcobarbital, nimetazepam, nitrazepam, oxcarbazepine, paramethadione, phenacemide, phenetharbital, pheneturide, phenobarbital, phensuximide, phenylmethylbarbituric acid, phenytoin, phethenylate sodium, potassium bromide, pregabaline, primidone, progabide, sodium bromide, solanum, strontium bromide, suclofenide, sulthiame, tetrantoin, tiagabine, topiramate, trimethadione, valproic acid, valpromide, vigabatrin, zonisamide, a pharmaceutically acceptable derivative thereof, or any mixture thereof.

Examples of useful Ca^{2+}-channel blockers include, but are not limited to, bepridil, clentiazem, diltiazem, fendiline, gallopamil, mibefradil, prenylamine, semotiadil, terodiline, verapamil, amlodipine, aranidipine, barnidipine, benidipine, cilnidipine, efonidipine, elgodipine, felodipine, isradipine, lacidipine, lercanidipine, manidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, cinnarizine, flunarizine, lidoflazine, lomerizine, bencyclane, etafenone, fantofarone, perhexiline, a pharmaceutically acceptable derivative thereof, or any mixture thereof.

Examples of useful therapeutic agents for treating or preventing UI include, but are not limited to, propantheline, imipramine, hyoscyamine, oxybutynin, dicyclomine, a pharmaceutically acceptable derivative thereof, or any mixture thereof.

Examples of useful therapeutic agents for treating or preventing anxiety include, but are not limited to, benzodiazepines, such as alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, demoxepam, diazepam, estazolam, flumazenil, flurazepam, halazepam,

lorazepam, midazolam, nitrazepam, nordazepam, oxazepam, prazepam, quazepam, temazepam, and triazolam; non-benzodiazepine agents, such as buspirone, gepirone, ipsapirone, tiospirone, zolpicone, zolpidem, and zaleplon; tranquilizers, such as barbituates, *e.g.*, amobarbital, aprobarbital, butabarbital, butalbital, mephobarbital, methohexital, pentobarbital, phenobarbital, secobarbital, and thiopental; propanediol carbamates, such as meprobamate and tybamate; a pharmaceutically acceptable derivative thereof; or any mixture thereof.

Examples of useful therapeutic agents for treating or preventing diarrhea include, but are not limited to, diphenoxylate, loperamide, a pharmaceutically acceptable derivative thereof, or any mixture thereof.

Examples of useful therapeutic agents for treating or preventing epilepsy include, but are not limited to, carbamazepine, ethosuximide, gabapentin, lamotrigine, phenobarbital, phenytoin, primidone, valproic acid, trimethadione, benzodiazepines, γ vinyl GABA, acetazolamide, felbamate, a pharmaceutically acceptable derivative thereof, or any mixture thereof.

Examples of useful therapeutic agents for treating or preventing drug abuse include, but are not limited to, methadone, desipramine, amantadine, fluoxetine, buprenorphine, an opiate agonist, 3-phenoxypyridine, levomethadyl acetate hydrochloride, serotonin antagonists, a pharmaceutically acceptable derivative thereof, or any mixture thereof.

Examples of non-steroidal anti-inflammatory agents, 5-lipoxygenase inhibitors, anti-emetics, β-adrenergic blockers, antidepressants, and anti-cancer agents are known in the art and can be selected by those skilled in the art. Examples of useful therapeutic agents for treating or preventing memory disorder, obesity, constipation, cough, high blood pressure, anorexia/cachexia, an ulcer, IBD, IBS, addictive disorder, Parkinson's disease and parkinsonism, a stroke, a seizure, a pruritic condition, psychosis, Huntington's chorea, ALS, a cognitive disorder, a migraine, dyskinesia, depression, and/or treating, preventing or inhibiting vomiting include those that are known in the art and can be selected by those skilled in the art.

A Substituted-Quinoxaline-Type Bridged-Piperidine Compound and the second therapeutic agent combined can act either additively or synergistically to treat the same Condition, or they may act independently of each other such that the Substituted-Quinoxaline-Type Bridged-Piperidine Compound treats or prevents a first Condition and the second therapeutic agent treats or prevents a second disorder, which can be the same as the first Condition or another disorder. In one embodiment, a Substituted-Quinoxaline-Type Bridged-Piperidine Compound is administered concurrently with a second therapeutic agent as a single composition comprising an effective amount of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound and an effective amount of the second therapeutic agent. Alternatively, a composition comprising an effective amount of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound and a second composition

comprising an effective amount of the second therapeutic agent are concurrently administered. In another embodiment, an effective amount of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound is administered prior or subsequent to administration of an effective amount of the second therapeutic agent. In this embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound is administered while the second therapeutic agent exerts its therapeutic effect, or the second therapeutic agent is administered while the Substituted-Quinoxaline-Type Bridged-Piperidine Compound exerts its therapeutic effect for treating or preventing a Condition.

A composition of the invention is prepared by a method comprising admixing a Substituted-Quinoxaline-Type Bridged-Piperidine Compound or a pharmaceutically acceptable derivative thereof with a pharmaceutically acceptable carrier or excipient. Admixing can be accomplished using methods known for admixing a compound (or derivative) and a pharmaceutically acceptable carrier or excipient. In one embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound is present in the composition in an effective amount.

4.8 Kits

The invention further provides kits that can simplify the handling and administration of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound to an animal.

A typical kit of the invention comprises a unit dosage form of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound. In one embodiment, the unit dosage form comprises a first container, which can be sterile, containing an effective amount of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound and a pharmaceutically acceptable carrier or excipient. The kit can further comprise a label or printed instructions instructing the use of the Substituted-Quinoxaline-Type Bridged-Piperidine Compound to treat or prevent a Condition. The kit can further comprise a unit dosage form of a second therapeutic agent, for example, a second container containing an effective amount of the second therapeutic agent and a pharmaceutically acceptable carrier or excipient. In another embodiment, the kit comprises a container containing an effective amount of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound, an effective amount of a second therapeutic agent and a pharmaceutically acceptable carrier or excipient. Examples of second therapeutic agents include, but are not limited to, those listed above.

Kits of the invention can further comprise a device that is useful for administering the unit dosage forms. Examples of such a device include, but are not limited to, a syringe, a drip bag, a patch, an inhaler, and an enema bag.

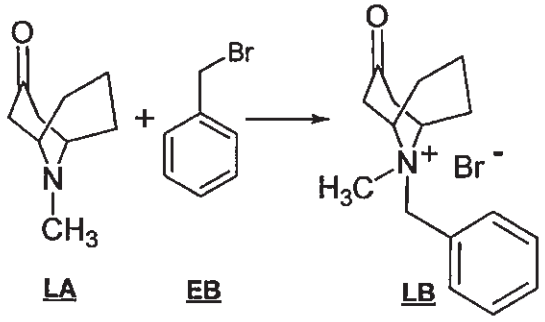
The invention relates to methods for preparing Substituted-Quinoxaline-Type Bridged-Piperidine Compounds and/or pharmaceutically acceptable derivatives thereof, such as illustrated in the following examples. The following examples are set forth to assist in understanding the

invention and should not be construed as specifically limiting the invention described and claimed herein. Such variations of the invention, including the substitution of all equivalents now known or later developed, that would be within the purview of those skilled in the art, and changes in formulation or changes in experimental design, are to be considered to fall within the scope of the invention incorporated herein.

5. EXAMPLES

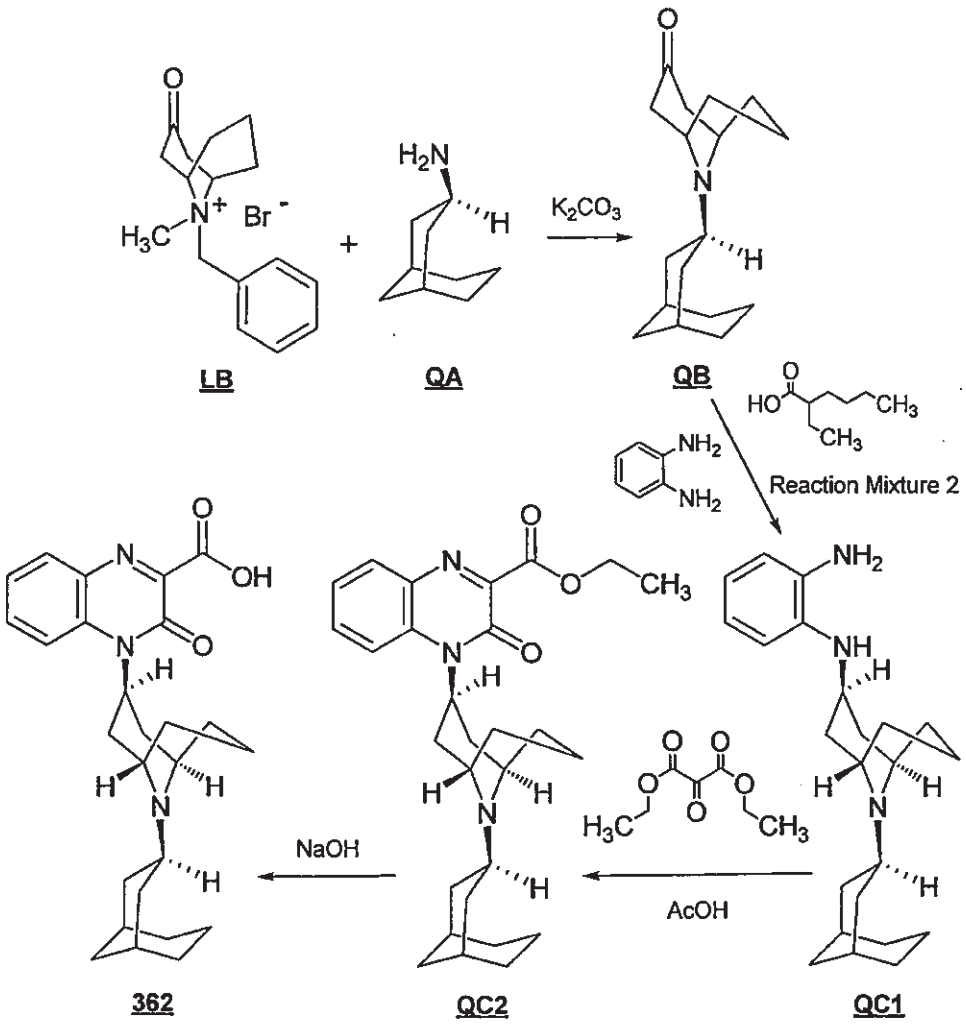
The following examples illustrate various aspects of the invention, and are not to be construed to limit the claims in any manner whatsoever.

5.1 Example 1



LA EB LB

A mixture of the compound of formula LA (10.00g, 65.4mmol, Trans World Chemicals, Inc., Rockville, MD) and the compound of formula EB, (bromomethyl)benzene (17g, 65.4mmol, Sigma-Aldrich, St. Louis, MO) was refluxed in acetone (150mL) for 3h, cooled, filtered, washed twice with Et_2O (30mL for each wash), washed twice with hexanes (30mL for each wash), and dried under reduced pressure to provide 10g of the compound of formula LB, 9-methyl-9-benzyl-9-azabicyclo[3.3.1]nonan-3-one bromide, as white solid (yield 47%).



To a mixture of the compound of formula **QA** ((*exo*)-bicyclo[3.3.1]nonan-3-amine, 1222mg, 8.78mmol), K_2CO_3 (121.3mg, 0.878mmol), EtOH (10mL), and water (3mL) at a temperature of about 25°C was added a mixture of the compound of formula **LB** (2846mg, 8.78mmol), EtOH (14mL), and water (16mL). After the addition, the resulting reaction mixture was heated to a temperature of 90°C and stirred for 4h. Thereafter, the reaction mixture was cooled to a temperature of about 25°C and ice-water (50mL) was poured into the reaction mixture to provide a colorless precipitate. To the precipitate was added saturated aqueous $NaHCO_3$ (10mL). The mixture was sonicated; a precipitate formed. The precipitate was filtrated, washed twice with water (8mL for each wash), and dried at 70°C for 8h under reduced pressure to provide 1020mg of the compound of formula **QB** as a colorless solid (yield 45%).

The identity of the compound of formula **QB**, 9-((*exo*)-bicyclo[3.3.1]nonan-3-yl)-9-azabicyclo[3.3.1]nonan-3-one, was confirmed using ^1H NMR and LC/MS.

Compound **QB**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 1.26 (s, 1H), 1.43-1.69 (m, 13H), 1.85 (m, 2H), 2.01 (m, 4H), 2.22 (d, 2H), 2.63 (dd, J=16.42, 6.32Hz, 2H), 3.35-3.41 (m, 1H), 3.69 (s, 2H); LC/MS: *m/z*=262.1 $[M+H]^+$ (Calc: 261).

Under a nitrogen atmosphere, to a solution of the compound of formula **QB** (1020mg, 3.90mmol) in CH_2Cl_2 (15mL) at a temperature of about 25°C was added 1,2-phenylenediamine (1266mg, 11.71mmol, Sigma-Aldrich) and 2-ethylhexanoic acid (0.938mL, 5.85mmol, Sigma-Aldrich). The mixture was stirred at a temperature of about 25°C for 30min to provide reaction mixture 1.

Under a nitrogen atmosphere, to a solution of sodium tetrahydroborate (590mg, 15.61mmol, Sigma-Aldrich) in CH_2Cl_2 (10mL) at a temperature of about 25°C was added 2-ethylhexanoic acid (8.75mL, 54.6mmol). The mixture was stirred at a temperature of about 25°C for 30min to provide reaction mixture 2.

Under a nitrogen atmosphere, to reaction mixture 1 at 0°C was added reaction mixture 2 dropwise over a 15min period. After the addition, the resulting reaction mixture was heated to a temperature of about 25°C and stirred for 30min. Thereafter, the reaction mixture was heated to a temperature of 60°C and stirred for 16h. After cooling the reaction mixture to a temperature of about 25°C, saturated aqueous $NaHCO_3$ (20mL) was added, the mixture stirred for 10min, then extracted twice with 1M aqueous K_2CO_3/EtOAc (200mL for each extraction). The organic portions were combined, dried (Na_2SO_4), and concentrated under reduced pressure to provide a brown solid. The solid was chromatographed with an amino-silica gel column (Yamazen Corp. W091-01) eluted with a gradient of from 0%:100% EtOAc:n-hexane to 30%:70% EtOAc:n-hexane to provide 815mg of the compound of formula **QC1** as a colorless solid (yield 59%).

The identity of the compound of formula **QC1**, *N*^{1}-((*endo*)-9-((*exo*)-bicyclo[3.3.1]nonan-3-yl)-9-azabicyclo[3.3.1]nonan-3-yl)benzene-1,2-diamine, was confirmed using ^{1}H NMR and LC/MS.

Compound **QC1**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 1.02-1.83 (m, 17H), 2.01 (m, 5H), 2.40-2.48 (m, 2H), 3.06-3.45 (m, 6H), 3.76 (br, 1H), 6.61-6.82 (m, 4H); LC/MS: *m/z*=354.1 $[M+H]^+$ (Calc: 353).

Under a nitrogen atmosphere, to a solution of the compound of formula **QC1** (815mg, 2.305mmol) in toluene (16mL) at a temperature of about 25°C was added diethyl 2-oxomalonate (0.407mL, 2.54mmol, Sigma-Aldrich) and AcOH (0.145mL, 2.54mmol). After the addition, the resulting reaction mixture was heated to a temperature of 130°C and stirred for 1h. Thereafter, the reaction mixture was cooled to a temperature of about 25°C and concentrated under reduced pressure to provide a sticky oil. The oil was diluted with saturated aqueous $NaHCO_3$, extracted twice with $CHCl_3$:H_2O (100mL for each extraction), dried (Na_2SO_4), and concentrated under

reduced pressure to provide an orange solid. The solid was chromatographed with an amino-silica gel column (Yamazen Corp. W091-01) eluted with a gradient of from 0%:100% EtOAc:n-hexane to 20%:80% EtOAc:n-hexane to provide 560mg of the compound of formula **QC2** as a colorless solid (yield 52%).

The identity of the compound of formula **QC2**, ethyl 4-((*endo*)-9-((*exo*)-bicyclo[3.3.1]nonan-3-yl)-9-azabicyclo[3.3.1]nonan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

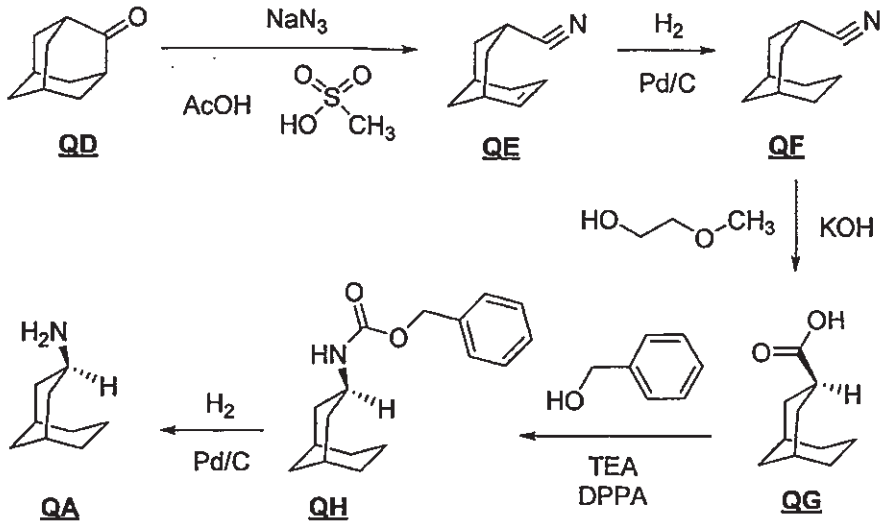
Compound **QC2**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 1.04-1.11 (m, 2H), 1.35-1.86 (m, 17H), 1.92-2.02 (m, 6H), 2.37-2.47 (m, 1H), 2.67-2.79 (m, 1H), 3.46-3.56 (m, 3H), 4.51 (q, J=7.07Hz, 2H), 5.20 (m, 1H), 7.34-7.37 (m, 1H), 7.63 (t, J=6.57Hz, 2H), 7.92 (d, J=8.08Hz, 1H); LC/MS: *m/z*=464.2 $[M+H]^+$ (Calc: 463).

To a suspension of the compound of formula **QC2** (561mg, 1.21mmol) in EtOH (15mL) at a temperature of about 25°C was added 2N aqueous NaOH (1.812mL, 3.62mmol). The resulting reaction mixture was stirred at a temperature of about 25°C for 1h. Thereafter, the reaction mixture was concentrated under reduced pressure to provide a residue. The residue was diluted with water (10mL) to form a colorless solution, neutralized with 2N aqueous HCl (2.3mL), and sonicated to provide a white precipitate. The precipitate was collected by filtration, washed with water, and dried at 75°C for 5h under reduced pressure to provide 396mg of Substituted-Quinoxaline-Type Bridged-Piperidine Compound **362** as a colorless solid (yield 75%).

The identity of Substituted-Quinoxaline-Type Bridged-Piperidine Compound **362**, 4-((*endo*)-9-((*exo*)-bicyclo[3.3.1]nonan-3-yl)-9-azabicyclo[3.3.1]nonan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Bridged-Piperidine Compound **362**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 0.83 (dq, J=8.72, 2.78Hz, 1H), 1.22 (s, 1H), 1.38 (br, 1H), 1.54 (d, J=12.63Hz, 1H), 1.69 (s, 6H), 1.87 (m, 4H), 2.05 (t, J=13.89Hz, 2H), 2.22 (s, 2H), 2.51 (dd, J=19.71, 11.12Hz, 2H), 2.70 (m, 3H), 2.98 (t, J=12.38Hz, 2H), 4.11-4.22 (m, 3H), 6.65 (br, 1H), 7.51-7.62 (m, 4H), 7.93 (t, J=7.83Hz, 1H), 8.16 (d, J=8.08Hz, 1H), 8.96 (dd, J=7.83, 6.32Hz, 1H), 10.89 (s, 1H); LC/MS (100%, t_r=1.55min): *m/z*=436.2 $[M+H]^+$ (Calc: 436).

Taking into account the procedures provided in J.A. Peters, J.M. Van Der Toorn and H. Van Bekkumm, *Tetrahedron* 31:2273-2281 (1975) and "Diphenylphosphoryl azide a new convenient reagent for a modified Curtius rearrangement and for peptide synthesis," T. Shioiri, K. Ninomiya, S. Yamada, *J. Amer. Chem. Soc.* 94:6202-6205 (1972), the compound of formula **QA** was prepared as follows.



Under a nitrogen atmosphere, to a solution of the compound of formula **QD** (adamantane-2-one, 60g, 399mmol, Sigma-Aldrich) in AcOH (251mL, 4394mmol) and methane sulfonic acid (182.00mL, 2803mmol, Sigma-Aldrich) at a temperature of 20°C was added sodium azide (29.9g, 459mmol) portionwise over 45min. After the addition, the resulting reaction mixture was stirred for 30min at a temperature of from 20°C to 25°C. Thereafter, ice-water (1L) was poured into the reaction mixture to provide a white precipitate that was collected by filtration, washed with water (400mL), and dried at 60°C for 4h under reduced pressure to provide 40.78g of the compound of formula **QE** as a colorless solid (yield 69%).

The identity of the compound of formula **QE**, bicyclo[3.3.1]non-6-ene-3-carbonitrile, was confirmed using ^{1}H NMR.

Compound **QE**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 1.53 (d, J=12.67Hz, 1H), 1.72-2.05 (m, 5H), 2.23 (dt, J=17.91Hz, 8.11Hz, 2H), 2.41-2.50 (m, 2H), 2.96 (dd, J=9.63, 4.06Hz, 1H), 5.85-5.95 (m, 2H).

Under a hydrogen atmosphere, a mixture of the compound of formula **QE** (5260mg, 35.7mmol), 10% palladium on carbon (570mg, 0.536mmol, Sigma-Aldrich), and MeOH (150mL) was stirred at a temperature of about 25°C for 4h. After the Pd/C was filtered off, the mixture was concentrated under reduced pressure to provide a colorless oil. The oil was chromatographed with a silica gel column eluted with a gradient of from 3%:97% EtOAc:n-hexane to 20%:80% EtOAc:n-hexane to provide 3500mg of the compound of formula **QF** as a colorless solid (yield 66%).

The identity of the compound of formula **QF**, bicyclo[3.3.1]nonane-3-carbonitrile, was confirmed using ^{1}H NMR.

Compound **QF**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 1.22 (m, 1H), 1.38-1.59 (m, 8H), 1.72-1.82 (m, 1H), 2.04-2.08 (m, 2H), 2.20-2.28 (m, 2H), 2.60-2.69 (m, 1H).

Under a nitrogen atmosphere, to a solution of the compound of formula **QF** (2530mg, 16.95mmol) in 2-methoxyethanol (26.9mL, 339mmol) at a temperature of about 25°C was added KOH (4280mg, 76mmol). After the addition, the resulting reaction mixture was heated to a temperature of 120°C and stirred for 16h. Thereafter, the reaction mixture was cooled to a temperature of about 25°C, 2N aqueous HCl was added such that the pH was within 3 to 4, and a pale brown precipitate formed. The precipitate was collected by filtration, washed with water, and dried at 70°C for 3h under reduced pressure to provide a pale brown solid, which ^{1}H NMR showed to be a 1:9 mixture of *endo*:*exo* isomers.

Under a nitrogen atmosphere, to a solution of the above *endo*:*exo* isomer mixture in 2-methoxyethanol (73.5mL, 932mmol) at a temperature of about 25°C was added KOH (4756mg, 85mmol). After the addition, the resulting reaction mixture was heated to a temperature of 120°C and stirred for 16h. Thereafter, the reaction mixture was cooled to a temperature of about 25°C, 2N aqueous HCl was added such that the pH was within 3 to 4, and a pale brown precipitate formed. The precipitate was collected by filtration, washed with water, and dried at 70°C for 3h under reduced pressure to provide 2187mg of the compound of formula **QG** as a pale brown solid, with a melting point of 126-128°C and present only as the *exo* isomer (yield 77%).

The identity of the compound of formula **QG**, (*exo*)-bicyclo[3.3.1]nonane-3-carboxylic acid, was confirmed using ^{1}H NMR.

Compound **QG**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 1.52-1.85 (m, 10H), 1.96 (t, J=6.59Hz, 4H), 3.10-3.19 (m, 1H).

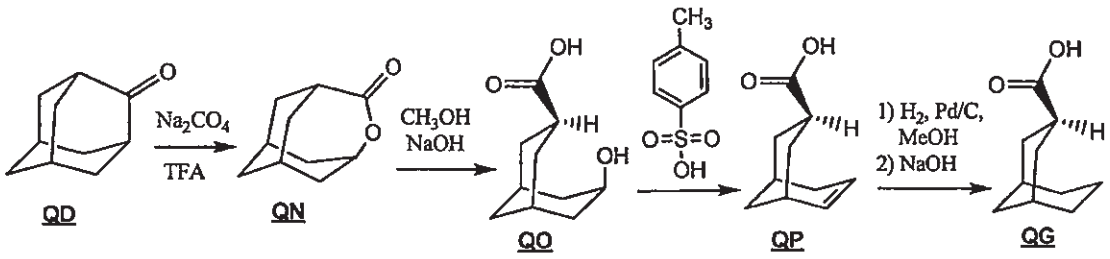
Under a nitrogen atmosphere, to a solution of the compound of formula **QG** (2680mg, 15.93mmol) in toluene (25mL) at a temperature of about 25°C was added TEA (2.65mL, 19.12mmol, Sigma-Aldrich) and DPPA (4.51mL, 19.12mmol, Sigma-Aldrich). After the addition, the resulting reaction mixture was heated to a temperature of 70°C and stirred for 1h. Thereafter, the reaction mixture was cooled to a temperature of about 25°C and concentrated under reduced pressure to provide a pale yellow oil, which was dried under reduced pressure at a temperature of about 25°C. To the oil was added phenylmethanol (4.77mL, 45.9mmol, Sigma-Aldrich). After the addition, the resulting reaction mixture was heated to a temperature of 90°C and stirred for 1.5h. Thereafter, the reaction mixture was cooled to a temperature of about 25°C and chromatographed with a silica gel column eluted with a gradient of from 2%:98% EtOAc:n-hexane to 10%:90% EtOAc:n-hexane to provide 4270mg of the compound of formula **QH** as a colorless solid (yield 98%).

The identity of the compound of formula **QH**, benzyl (*exo*)-bicyclo[3.3.1]nonan-3-ylcarbamate, was confirmed using ^{1}H NMR and LC/MS.

Compound **QH**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 1.32 (td, J=12.25, 3.71Hz, 2H), 1.44-1.80 (m, 8H), 1.97-2.09 (m, 4H), 4.28-4.46 (m, 2H), 5.08 (s, 2H), 7.26-7.35 (m, 5H); LC/MS: *m/z*=274.2 $[M+H]^+$ (Calc: 273).

Under a hydrogen atmosphere, a mixture of the compound of formula **QH** (4456mg, 16.30mmol), 10% palladium on carbon (694mg, 0.652mmol), and EtOH (50mL) was stirred at a temperature of about 25°C for 3h. After filtering off the Pd/C and washing with EtOH, the mixture was concentrated under reduced pressure to a volume of 20mL. The EtOH solution contained 2270mg (16.30mmol) of the compound of formula **QA**.

Alternatively, the compound of formula **QG** was prepared from the compound of formula **QD** as follows.



The compound of formula **QD** (200g, 1.33mol) was dissolved in 2,2,2-trifluoroacetic acid (1L, Sigma-Aldrich) and cooled to 0°C by an ice/MeOH bath. To this mechanically-stirred mixture was added sodium percarbonate (417.64g, 2.66mol) portionwise such that the temperature of the reaction mixture was kept below 5°C. The cold bath was removed and the reaction mixture was allowed to warm to a temperature of about 25°C. After 2.5h stirring at about 25°C, deionized water (1L) was added over 5min followed by the addition of DCM (2L). The DCM layer was separated, dried ($MgSO_4$), filtered, and concentrated to dryness under reduced pressure to provide 209g of the compound of formula **QN** as a white crystalline solid (yield 95%).

The identity of the compound of formula **QN**, 4-oxa-tricyclo[4.3.1.1*3,8*]undecan-5-one, was confirmed using ^{1}H NMR and TLC.

Compound **QN**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 4.48 (1H, s), 3.06 (1H, m), 2.09 (2H, m), 2.00 (3H, m), 1.95 (2H, m), 1.81 (2H, m), 1.70 (2H, m); TLC (SiO_2, 1:1 EtOAc:hexanes) R_f=0.8 (visualized with molybdenum blue spray reagent).

To a mixture of the compound of formula **QN** (165.52g, 1.0 mol) and MeOH (200mL) was added 10M NaOH (600mL). Thereafter, with stirring the resulting reaction mixture was heated at reflux for 24h. After cooling to a temperature of about 25°C, the mixture was concentrated under reduced pressure and deionized water (4L) was added. The resulting solution was stirred and acidified with concentrated HCl to a pH of about 2.5. The white precipitate that formed was

allowed to stir with ice bath cooling for 1h and then filtered under reduced pressure to provide the partially dried compound of formula **QO**.

The identity of the compound of formula **QO**, *exo*-7-hydroxybicyclo[3.3.1]nonane-3-carboxylic acid, was confirmed using ^{1}H NMR and TLC.

Compound **QO**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 11.88 (1H, s), 4.44 (1H, s), 3.73 (1H, m), 1.95 (4H, m), 1.63 (2H, m), 1.41 (3H, m), 1.22 (2H, m), 1.16 (1H, m); TLC (SiO_2, 2:1:0.1 EtOAc:hexanes:AcOH) R_f=0.3 (visualized with molybdenum blue spray reagent). The ^{1}H-NMR indicated that the compound of formula **QO** was about 97% to 98% pure and nuclear Overhauser enhancement spectroscopy ("NOESY") NMR indicated only the *exo*-isomer was present.

The compound of formula **QO** from the step above was suspended in toluene (1.2L) and to this was added TsOH (35.6mL, 0.5mol, Sigma-Aldrich). With stirring the resulting reaction mixture was heated to reflux with azeotropic removal of water for 2h. After cooling to a temperature of about 25°C, deionized water (1L) was added. The toluene layer was separated, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide the compound of formula **QP**, which could be if desired but which was not recrystallized from cyclohexane.

The identity of the compound of formula **QP**, *exo*-bicyclo[3.3.1]non-6-ene-3-carboxylic acid, was confirmed using ^{1}H NMR and TLC.

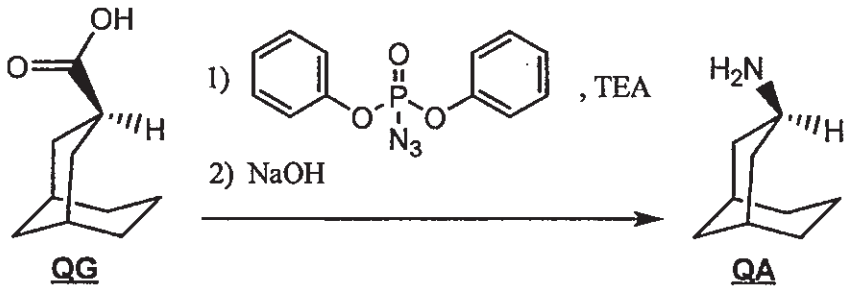
Compound **QP**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 10.45 (1H, bs), 5.85 (1H, m), 5.70 (1H, m), 2.79 (1H, m), 2.37 (2H, m), 2.11 (1H, m), 1.81 (3H, m), 1.61 (4H, m); TLC (SiO_2, 1:1:0.1 EtOAc:hexanes:AcOH) R_f=0.8 (visualized with molybdenum blue spray reagent). The ^{1}H-NMR indicated that the compound of formula **QP** was about 97% to 98% pure and NOESY indicated only the *exo*-isomer was present.

The compound of formula **QP** from the step above was added to 6:1 EtOAc:MeOH (700mL). This mixture was split into two batches and to each batch was added 10% palladium on carbon (0.01mol). Under a 50psi hydrogen atmosphere, each batch was stirred at a temperature of about 25°C for 2h. The batches were combined, filtered through CELITE, and concentrated to dryness under reduced pressure at 50°C to provide a cream colored sticky solid which was determined to be a mixture of the desired product and its methyl ester. To the solid was added MeOH (600mL) and 3M NaOH (300mL). The resulting reaction mixture was stirred at a temperature of about 25°C for 1h. The mixture was poured into deionized water (3L) and concentrated HCl was added until the pH was about 2. Then DCM (3L) was added. The resulting layers were separated and the aqueous layer was washed with DCM (2L). The organic portions were combined, dried ($MgSO_4$), filtered, and concentrated to dryness under reduced pressure to provide 147.34g of the compound of formula **QG** as a white crystalline solid (yield 88% for three steps).

The identity of the compound of formula QG was confirmed using ^{1}H NMR and TLC.

Compound QG: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 9.25 (1H, bs), 3.13 (1H, m), 1.97 (4H, m), 1.80 (2H, m), 1.70 (5H, m), 1.57 (3H, m); TLC (SiO_2, 1:1:0.1 EtOAc:hexanes:AcOH) R_f=0.8 (visualized with molybdenum blue spray reagent).

Alternatively, the compound of formula QA was prepared from the compound of formula QG as follows.



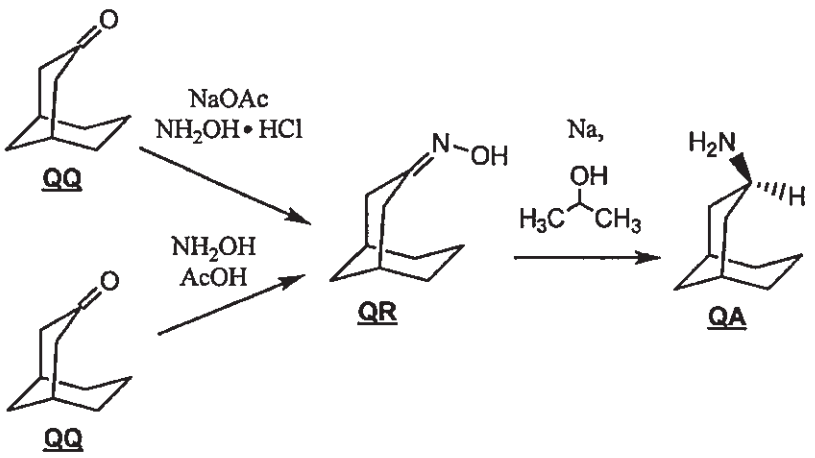
QG QA

Under an argon atmosphere, to a solution of the compound of formula QG (5.23g, 31.13mmol) in toluene (50mL) at a temperature of about 25°C was added TEA (4.77mL, 34.24mmol) and DPPA (7.40mL, 34.24mmol). After the addition, the resulting reaction mixture was heated to a temperature of 75°C and stirred for 1h. Thereafter, the reaction mixture was cooled to a temperature of 70°C and concentrated to dryness under reduced pressure to provide a yellow oil. The oil was cooled to 5°C and THF (50mL) was added. While stirring, the mixture was further cooled to 0°C and a solution of NaOH (3.73g, 93.39mmol) in deionized water (25mL) was added dropwise over 15min while maintaining the temperature of the reaction mixture below 5°C. The reaction mixture was stirred for 1h at 0°C then treated with concentrated HCl until the pH was about 8. Deionized water (100mL) was added; a white precipitate formed. The mixture was stirred an additional 30min at 0°C. The precipitate was collected by filtration under reduced pressure then suspended in 1:1 1M NaOH:Et_2O (500mL). The mixture was stirred until all solids disappeared. Upon ending stirring, the layers that formed were separated and the aqueous layer was washed with Et_2O (250mL). The organic portions were combined, dried ($MgSO_4$), and filtered. To the filtrate was added 2M HCl in Et_2O (38mL, 77.83mmol); a white solid formed. The mixture was cooled to -5°C and stirred an additional 1h. The solid was collected by filtration and dried under reduced pressure at 50°C to provide 4.1g of the compound of formula QA as the diphenylphosphate salt (yield 75%).

The identity of the compound of formula QA was confirmed using ^{1}H NMR and TLC.

Compound QA: ^{1}H NMR: δ_H (400MHz, CD_3OD): 3.91 (1H, m), 2.08 (4H, m), 1.71 (4H, m), 1.59 (6H, m); TLC (SiO_2, 1:1:0.1 DCM:MeOH:NH_3) R_f=0.4 (visualized with molybdenum blue spray reagent).

Alternatively, taking into account the procedures provided in F.I. Carroll, M.S. Melvin, M.C. Nuckols, S.W. Mascarella, H.A. Navarro, and J.B. Thomas, *J. Med. Chem.* 49:1781-1791 (2006), the compound of formula **QA** was prepared from the compound of formula **QQ** as follows.



Under a nitrogen atmosphere, to a solution of the compound of formula **QQ** (bicyclo[3.3.1]nonan-3-one, 975mg, 7.05mmol) in EtOH (40mL) at a temperature of about 25°C was added sodium acetate (1,157mg, 14.11mmol, Sigma-Aldrich) and hydroxylamine hydrochloride (980mg, 14.11mmol, Sigma-Aldrich). The resulting reaction mixture was stirred at a temperature of about 25°C for 2h. Thereafter, the mixture was diluted with saturated aqueous $NaHCO_3$ then extracted three times with EtOAc (30mL for each extraction). The organic portions were combined, washed with saturated aqueous NaCl, dried ($MgSO_4$), and evaporated under reduced pressure to provide 800mg of the compound of formula **QR** as a yellow solid (yield 76%).

The identity of the compound of formula **QR**, bicyclo[3.3.1]nonan-3-one oxime, was confirmed using ^1H NMR.

Compound **QR**: ^1H NMR: δ_H ($CDCl_3$): 1.40 (m, 1H), 1.50-1.80 (m, 8H), 1.99-2.17 (m, 3H), 2.40 (d, J=8.0Hz, 2H), 3.20 (d, J=16Hz, 1H).

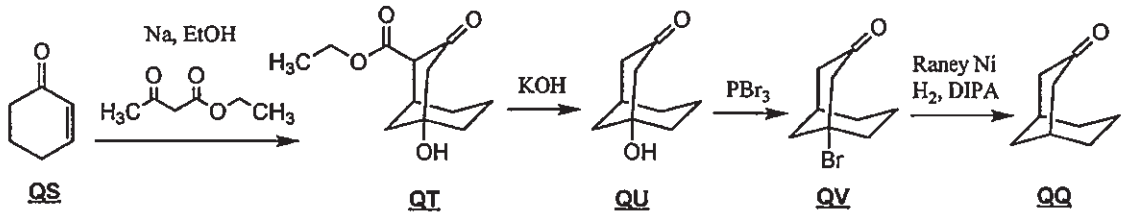
Alternatively, the compound of formula **QR** was prepared from the compound of formula **QQ** as follows. To a solution of the compound of formula **QQ** (390g, 2.822mol) in dry THF (2L) at a temperature of about 25°C was added 50% aqueous hydroxylamine (207.5mL, 3.386mol, Sigma-Aldrich) followed by acetic acid (204mL, 3.386mol); thereafter, the temperature of the resulting reaction mixture rose to 35°C. While stirring, the reaction mixture was heated at 40°C for 2h. The mixture was poured into water (2L) and neutralized with sodium bicarbonate. The organic portion was separated and the aqueous portion was extracted with EtOAc (2L). The organic portions were combined, dried ($MgSO_4$), and concentrated to dryness under reduced pressure to provide a residue. The residue was dried at 50°C for 16h under reduced pressure in a vacuum oven to provide 417g of the compound of formula **QR** as a white solid (yield 96.5%).

Under a nitrogen atmosphere, to a refluxing suspension of sodium (2.401g, 104mmol, Sigma-Aldrich) in toluene (20mL) at 115°C was added a mixture of the compound of formula **QR** (1.60g, 10.44mmol) and 2-propanol (8mL) dropwise over 30min. The reaction mixture was stirred at reflux for 2h. Additional 2-propanol (3mL) was added dropwise. The reaction mixture was refluxed until the sodium was consumed. Thereafter, the mixture was cooled to a temperature of about 25°C then quenched by the addition of water (20mL). The organic portion was separated and washed twice with 1N HCl (30mL for each wash). The acidic solution was made alkaline by the addition of 2N NaOH (50mL) and extracted three times with Et_2O (50m for each extraction). The organic portions were combined, washed with saturated aqueous NaCl (50mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to provide the compound of formula **QA**.

The identity of the compound of formula **QA** was confirmed using ^{1}H NMR.

Compound **QA**: ^{1}H NMR: δ_H ($CDCl_3$): 3.38 (m, 1H), 1.90 (m, 4H), 1.70-1.20 (m, 10H).

Taking into account the procedures provided in "Improved synthetic methods for bicyclo[3.3.1]nonan-3-one," T. Mosose and O. Muraoka, *Chem. Pharmaceut. Bull.* 26(1):288-295 (1978), the compound of formula **QQ** was prepared as follows.



QS **QT** **QU** **QV** **QQ**

Under a nitrogen atmosphere and with mechanical stirring, to EtOH (2L) was added small pieces of sodium (63.2g, 2.746mol). The resulting suspension was heated to reflux and stirred under gentle reflux conditions until the sodium dissolved (about 1h). Thereafter, ethyl 3-oxobutanoate (357.4g, 2.746mol, Sigma-Aldrich) was added and the mixture was stirred for 5min. Thereafter, the compound of formula **QS** (cyclohex-2-enone, 220g, 2.288mol, Sigma-Aldrich) was added dropwise over 30min. The resulting orange reaction mixture was stirred under reflux for 48h. This first batch of the mixture was concentrated under reduced pressure to about half its original volume and poured into crushed ice (about 2kg). The procedure above was repeated to provide a second batch. The two batches were combined, the mixture was acidified to a pH of 5 with concentrated HCl, and extracted twice with EtOAc (2L for each extraction). The organic portions were combined, dried ($MgSO_4$), and concentrated to dryness under reduced pressure to provide an orange oil. The oil was adsorbed onto silica gel (1kg) and applied to a flash chromatograph with a silica gel column (2kg) eluted with a gradient of from 0%:100% EtOAc:hexanes to 50%:50% EtOAc:hexanes to provide a yellow oil. The oil was dissolved in hexanes (1L). With mechanical stirring, the solution was cooled to -10°C by an ice/MeOH bath,

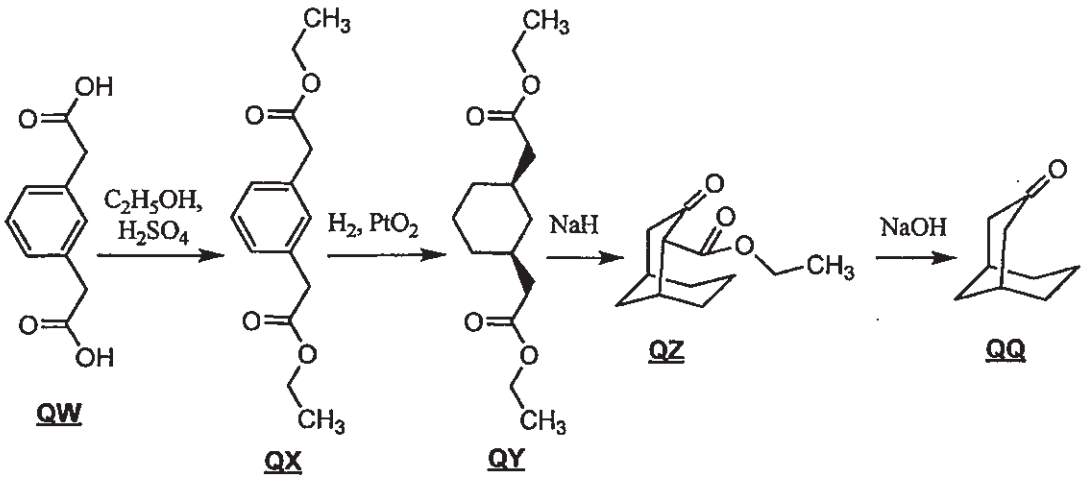
seeded with a crystal of the desired product, stirred for about 1h, then filtered and dried under reduced pressure to provide 753g of the compound of formula QT, ethyl 5-hydroxy-3-oxobicyclo[3.3.1]nonane-2-carboxylate, as a white solid (yield 73%).

The compound of formula QT (500g, 2.210mol) was dissolved in EtOH (2.5L). KOH (371.8g, 6.63mol) in water (2.5L) was added and the resulting reaction mixture was refluxed with stirring for 5.5h. The mixture was concentrated under reduced pressure to about half its original volume, poured into water (3L), and extracted twice with DCM (3L for each extraction). The organic portions were combined, dried ($MgSO_4$), and concentrated to dryness under reduced pressure to provide a yellow solid. The solid was dissolved in toluene (2L). The solution was mechanically-stirred for 1h then filtrated to provide 300g of the compound of formula QU, 1-hydroxybicyclo[3.3.1]nonan-3-one, as a pale yellow solid (yield 88%).

With mechanical stirring, the compound of formula QU (500g, 3.2425mol) was dissolved in dry DCM (2L) and cooled to -30°C. Phosphorus tribromide (965.5g, 3.5667mol, Sigma-Aldrich) in DCM (1L) was added portionwise over 30min. The resulting orange red solution allowed to warm slowly to 10°C over 3h. With mechanical stirring, the mixture was poured into crushed ice (3kg), diluted with hexanes (3L), and the organic portion was separated. The organic portion was washed with water (4L), washed with aqueous sodium bicarbonate solution (4L), dried ($MgSO_4$), and evaporated to dryness under reduced pressure to provide 570.5g of the compound of formula QV, 1-bromobicyclo[3.3.1]nonan-3-one, as pale yellow crystals which were dried under reduced pressure and then stored at below 0°C under argon (yield 81%). As it is relatively unstable, it is important that the organic portion be properly basified and also well dried or the compound of formula QV may decompose on standing. If an emulsion forms when using DCM, the reaction can be carried out in dry toluene instead to facilitate the work-up.

Raney nickel (about 10g, Sigma-Aldrich) was washed twice with dry THF (50mL for each wash) then suspended in dry THF (50mL). To this was added a mixture of the compound of formula QV (100g, 0.4604mol) and dry THF. Thereafter, diisopropylamine (DIPA, 71mL, Sigma-Aldrich) was added and under a hydrogen atmosphere and the resulting reaction mixture was shaken in a Parr Hydrogenator at 60psi for about 3h until no further hydrogen was taken up. It is important to ensure the reaction has gone substantially to completion before proceeding. This can be done using TLC (SiO_2, 1:1 hexanes:DCM) in which the compound of formula QQ has a slightly lower R_f than the compound of formula QV. Under a nitrogen atmosphere, the mixture was carefully filtered through CELITE, the filter pad washed with EtOAc (250mL), and the filtrate evaporated to dryness under reduced pressure to provide a light yellow gum. The gum was flash chromatographed with a silica gel column eluted with 5:1 hexanes:EtOAc to provide a white solid. The solid was crystallized at -30°C from hexanes (100mL) to provide 60g of the compound of formula QQ as a white solid (yield 95%).

Alternatively, taking into account the procedures provided in H.K. Hall, *J. Org. Chem.* 28:3213-3214 (1963), the compound of formula QQ was prepared as follows.



To a solution of the compound of formula QW (2,2'-(1,3-phenylene)diacetic acid, 50g, 0.26 mol, TCI-US, Portland, OR) in EtOH (500mL) at a temperature of about 25°C was added concentrated sulfuric acid (2mL). The resulting reaction mixture was refluxed for 24h. After cooling to a temperature of about 25°C, the mixture was concentrated to about 200mL under reduced pressure and diluted with toluene (400mL). The mixture was washed with water (100mL), washed with brine (100mL), and concentrated to dryness under reduced pressure to provide 63g of the compound of formula QX as a colorless oil (yield 98%).

The identity of the compound of formula QX, diethyl 2,2'-(1,3-phenylene)diacetate, was confirmed using ^{1}H NMR.

Compound QX: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 7.26-7.3 (m, 1H), 7.18-7.21 (m, 3H), 4.15 (q, J=7.1Hz, 4H), 3.6 (s, 4H), 1.25 (t, J=7.2Hz, 6H).

Under a hydrogen atmosphere, a mixture of the compound of formula QX (63g, 0.25 mol), platinum dioxide (2g, 0.09mol, Sigma-Aldrich), and acetic acid (250mL) at 30°C was degassed and stirred for 15h. The mixture was flushed with argon and diluted with water (40mL). The catalyst was removed by filtration. The mixture was concentrated under reduced pressure to about (200mL) then diluted with toluene (400mL). The mixture was washed twice with water (100mL for each wash), washed twice with $NaHCO_3$ (100mL for each wash), and washed with brine (100mL). The mixture was concentrated under reduced pressure to provide the compound of formula QY as a colorless oil.

The identity of the compound of formula QY, diethyl 2,2'-((*cis*)-cyclohexane-1,3-diyl)diacetate, was confirmed using ^{1}H NMR.

Compound **QY**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 4.15 (q, J=7.2Hz, 4H), 2.17 (d, J=7.0Hz, 4H), 1.4-1.9 (m, 6H), 1.25 (t, J=7.1Hz, 6H), 0.83-0.92 (m, 2H), 0.71 (dd, J=11.8, 11.9Hz, 2H).

The compound of formula **QY** from the step above was dissolved in dry DME (300mL). Sodium hydride (15g, Sigma-Aldrich) was added and the resulting suspension was heated at 94°C and stirred for 16h. After cooling to a temperature of about 25°C, the mixture was slowly poured into ice-water (500mL). The mixture was then extracted four times with EtOAc (200mL for each extraction). The organic portions were combined, washed with brine, and concentrated under reduced pressure to provide the compound of formula **QZ**, ethyl 3-oxobicyclo[3.3.1]nonane-2-carboxylate.

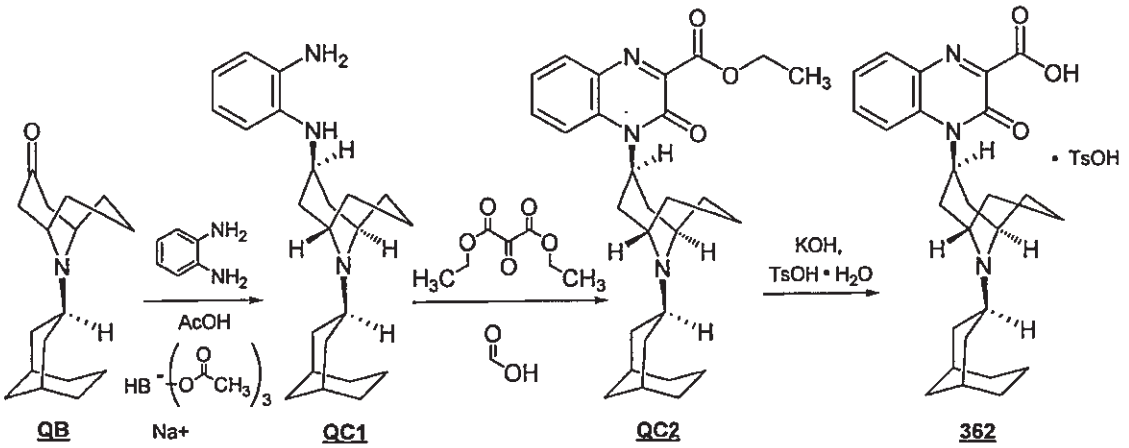
The compound of formula **QZ** from the step above was dissolved in EtOH (150mL). NaOH (30g, 0.75mol) in water (150mL) was added and the resulting reaction mixture was heated at 70°C for 8h. Thereafter, the mixture was concentrated under reduced pressure, diluted with brine (150mL), and extracted three times with Et_2O (150mL for each extraction). The organic portions were combined and concentrated to dryness under reduced pressure to provide 18g of the compound of formula **QQ** as a white solid (yield 51% for three steps).

The identity of the compound of formula **QQ** was confirmed using ^{1}H NMR.

Compound **QQ**: ^{1}H NMR: δ_H ($CDCl_3$): 2.52-1.31 (m, 6H), 1.82 (m, 2H), 1.70-1.56 (m, 5H), 1.54-1.32 (m, 2H).

5.2 Example 2

Substituted-Quinoxaline-Type Bridged-Piperidine Compound **362** was also prepared as follows.



Under a nitrogen atmosphere, to a solution of the compound of formula **QB** (15g, 57.38mmol) and

1,2-phenylenediamine (18.62g, 172.14mmol) in DME (38mL) at a temperature of about 25°C was added was added acetic acid (15mL). The mixture was stirred at a temperature of about 25°C for 16h to provide reaction mixture 3. To a suspension of sodium triacetoxy borohydride (42.56g, 200.53mmol) in DME (75mL) at a temperature of about 25°C was added dropwise reaction mixture 3 over 1h. The reaction mixture was diluted with additional DME (23mL) then stirred at a temperature of about 25°C for 5h. Thereafter, the reaction mixture was cooled to 0°C then water (75mL) was added dropwise over 30min while the temperature of the reaction mixture rose from 0°C to a temperature of about 25°C. The mixture was then extracted with $CHCl_3$:H_2O (225mL:75mL) and the $CHCl_3$ extract was washed with 10% aqueous AcOH (75mL). The aqueous portions were combined and extracted with $CHCl_3$ (75mL). Thereafter, the $CHCl_3$ portions were combined, dried (Na_2SO_4), and concentrated to dryness under reduced pressure to provide an oil. To the oil was added MeOH; the mixture was then concentrated under reduced pressure. The product was heated to 40°C and added was MeOH (45mL) and 8N NaOH (38mL) such that the pH was within 8 to 9 to provide a black solution. After seeding with a small amount of the desired product (the compound of formula **QC1**), a white precipitate formed. To the suspension containing the precipitate was added water (150mL) and MeCN (45mL) and the suspension was stirred at a temperature of about 25°C for about 1.5h. After filtration, the resulting solid was washed with 1:1 MeCN:H_2O (75mL) and dried under reduced pressure at a temperature of about 25°C to provide 12.05g of the compound of formula **QC1** (yield 59.4%). To the filtrate at a temperature of about 25°C was added 8N NaOH (1.5mL) and the filtrate was stirred for 1h to provide a white precipitate which was collected by filtration and washed with 1:1 MeCN:H_2O 1:1 (75mL) to provide an additional 3.93g of the compound of formula **QC1** (yield 19.4%; total yield 78.8%).

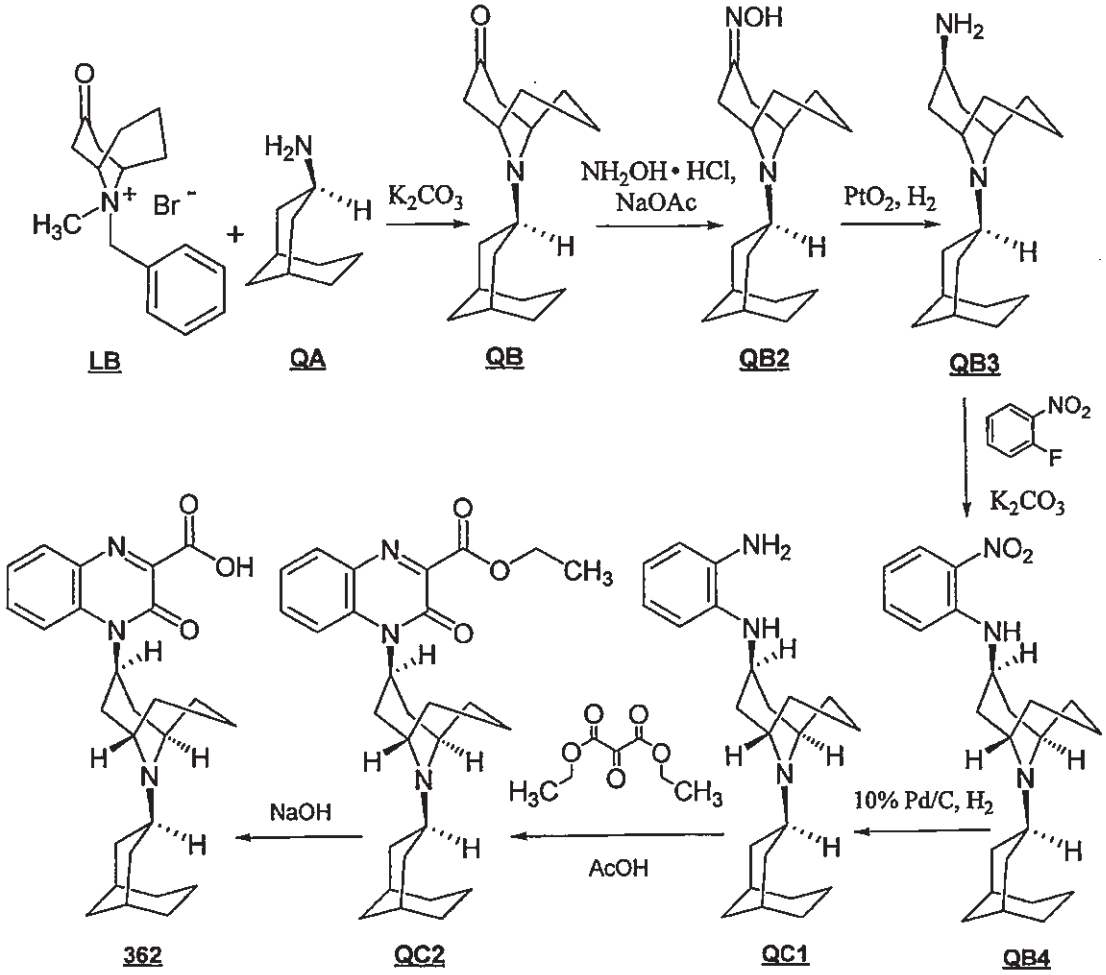
Under a nitrogen atmosphere, to a suspension of the compound of formula **QC1** (14g, 39.6mmol) in toluene (140mL) at a temperature of about 25°C was added diethyl 2-oxomalonate (8.28g, 47.52mmol) and formic acid (3.34mL, 87.12mmol). After the addition, the resulting reaction mixture was heated to a temperature within the range from 100°C to 110°C and stirred for about 75min. Thereafter, the reaction mixture was cooled to a temperature of 50°C and EtOAc (98mL) was added, followed by the addition of 5% aqueous $NaHCO_3$ (112mL) and THF (15mL) such that the pH of the mixture was within 6 to 7. The organic portion was separated and the aqueous portion extracted with EtOAc (102mL). The organic portions were combined, dried (Na_2SO_4), and concentrated to dryness under reduced pressure. The residue was dissolved in THF (50mL) at a temperature within the range from 50°C to 55°C. To the solution was added MeOH (280mL); a pale yellow precipitate formed at a temperature within the range from 40°C to 45°C. After cooling to about 25°C, water (70mL) was added to the suspension containing the precipitate. After filtration, the resulting solid was washed with MeOH (70mL) to provide a white solid which was dried under reduced pressure at a temperature of about 25°C to provide 13.69g of the compound of formula **QD** (yield 80.3%).

To a solution of the compound of formula **QC2** (500mg, 1.078mmol) in THF (5mL) at a temperature of about 25°C was added 8N KOH (0.202mL, 1.618mmol) in water (0.5mL). The resulting reaction mixture was stirred at a temperature of 80°C for 1h so that it was clear. After cooling the reaction mixture to a temperature between 40°C and 50°C, *para*-toluene sulfonic acid monohydrate (615mg, 3.24mmol, Sigma-Aldrich) in THF (2mL) was added. The clear mixture was stirred at a temperature of 50°C for 1h; a pale yellow precipitate formed. The precipitate was collected by filtration, washed twice with 4:1 THF:H_2O (5mL for each wash), and dried under reduced pressure at 100°C for 8h to provide 539mg of the tosylate salt of Substituted-Quinoxaline-Type Bridged-Piperidine Compound **362** as a pale yellow solid (yield 82%).

5.3 Example 3

Substituted-Quinoxaline-Type Bridged-Piperidine Compound **362** was also prepared as follows.

To a solution of the compound of formula **LA** (20.00g, 130.5mmol) in acetone (100mL) at a temperature of about 25°C was added the compound of formula **EB** (15.5mL, 130.55mmol). After the addition, the resulting reaction mixture was heated to reflux and refluxed for 24h. The mixture was cooled to a temperature of about 25°C and filtered to provide 34g of the compound of formula **LB** as a white solid (yield 81%).



To a solution of the compound of formula **QA** (1.453g, 10.44mmol) in EtOH (3.1mL) and water (0.7mL) at a temperature of about 25°C was added a mixture of K_2CO_3 (144mg, 1.04mmol), the compound of formula **LB** (4.06g, 12.53mmol), EtOH (29mL), and water (18mL). After the addition, the resulting reaction mixture was heated to a temperature of 90°C and stirred for 5h. Thereafter, the reaction mixture was cooled to a temperature of 0°C; a white precipitate formed. The precipitate was filtrated, rinsed with water, and collected to provide 1.58g of the compound of formula **QB** as a white solid (yield 58%).

The identity of the compound of formula **QB** was confirmed using ^{1}H NMR.

Compound **QB**: ^{1}H NMR: δ_H ($CDCl_3$): 1.50-1.70 (m, 14H), 1.75-1.90 (m, 2H), 1.90-2.10 (m, 4H), 2.20 (d, J=15.0Hz, 2H), 2.60 (m, 2H), 3.35 (m, 1H), 3.66 (m, 2H).

Under a nitrogen atmosphere, to a suspension of the compound of formula **QB** (10.77g, 41.2mmol) in EtOH (215mL) at a temperature of about 25°C was added hydroxylamine hydrochloride (4.29g, 61.8mmol) and sodium acetate (5.07g, 61.8mmol). The resulting reaction mixture was stirred at a temperature of about 25°C for 1.5h. Thereafter, the mixture was cooled to a temperature of about 25°C, quenched by the addition of water (50mL), then extracted twice with a

mixture of saturated aqueous $NaHCO_3$:$CHCl_3$ (200mL for each extraction). The organic portions were combined, dried (Na_2SO_4), and concentrated under reduced pressure to provide 11.39g of the compound of formula **QB2** as a pale yellow solid (yield > 99.5%).

The identity of the compound of formula **QB2**, 9-((*exo*)-bicyclo[3.3.1]nonan-3-yl)-9-azabicyclo[3.3.1]nonan-3-one oxime, was confirmed using LC/MS.

Compound **QB2**: LC/MS: *m/z*=277.45 $[M+H]^+$ (Calc: 276.42).

To a solution of the compound of formula **QB2** (11.39g, 41.2mmol) in AcOH (203mL) at a temperature of about 25°C was added platinum(IV) oxide (1.871g, 8.24mmol, Sigma-Aldrich). Under a hydrogen atmosphere at 5atm pressure, the resulting reaction mixture was stirred at a temperature of about 25°C for 24h. Thereafter, the mixture was filtered, washed with EtOAc (100mL), and concentrated under reduced pressure to provide a sticky yellow oil. Water was added to the oil and the mixture was neutralized by 28% aqueous ammonia to provide a white gel like precipitate. The mixture was then extracted twice with a mixture of $CHCl_3$:MeOH:H_2O (700mL for each extraction), dried ($MgSO_4$), and concentrated under reduced pressure to provide 9.07g of the *endo*-azabicyclo[3.3.1]nonan-3-amine form of the compound of formula **QB3** as a colorless solid (yield 84%).

The identity of the compound of formula **QB3**, 9-(*exo*-bicyclo[3.3.1]nonan-3-yl)-9-*endo*-azabicyclo[3.3.1]nonan-3-amine, was confirmed using ^{1}H NMR and LC/MS.

Compound **QB3**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 0.92-0.99 (m, 4H), 1.23-1.65 (m, 16H), 1.98 (m, 7H), 3.12 (s, 1H), 3.28 (s, 2H); LC/MS: *m/z*=263.15 $[M+H]^+$ (Calc: 262.43).

Under a nitrogen atmosphere, to a solution of the compound of formula **QB3** (9.07g, 34.6mmol) in DMF (136mL) at a temperature of about 25°C was added K_2CO_3 (7.16g, 51.8mmol) and 1-fluoro-2-nitrobenzene (3.65mL, 34.6mmol, Sigma-Aldrich). The resulting reaction mixture was heated at 100°C and stirred for 2h. Thereafter, the mixture was cooled to a temperature of about 25°C and quenched by the addition of ice-water (100mL) and saturated aqueous $NaHCO_3$ (10mL); a yellow precipitate formed. The precipitate was collected by filtration, washed twice with water (50mL for each wash), and dried at 70°C for 8h under reduced pressure to provide 11.98g of the compound of formula **QB4** as a yellow solid (yield 90%).

The identity of the compound of formula **QB4**, 9-((*exo*)-bicyclo[3.3.1]nonan-3-yl)-*N*-(2-nitrophenyl)-9-(*endo*)-azabicyclo[3.3.1]nonan-3-amine, was confirmed using ^{1}H NMR and LC/MS.

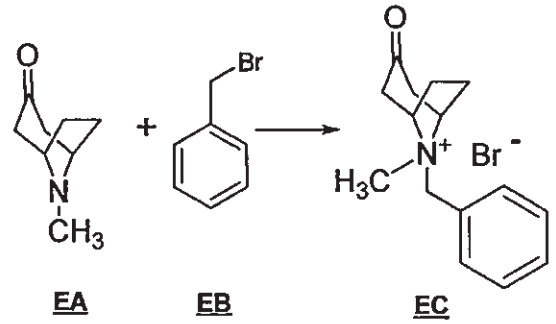
Compound **QB4**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 0.85-2.02 (m, 26H), 2.45 (m, 2H), 3.49 (m, 3H), 4.03 (t, J=3.79Hz, 1H), 6.58 (t, J=7.58Hz, 1H), 6.93 (d, J=8.08Hz, 1H), 7.40 (t, J=7.33Hz, 1H), 8.09 (dd, J=48.50, 7.58Hz, 2H); LC/MS: *m/z*=384.2 $[M+H]^+$ (Calc: 383.5).

Under a hydrogen atmosphere, to a suspension of the compound of formula **QB4** (11.98g, 31.2mmol) in MeOH (50mL) at a temperature of about 25°C was added 10% palladium on carbon (1.330g, 1.249mmol). After the addition, the resulting reaction mixture was stirred at a temperature of about 25°C for 1.5h. Thereafter, $CHCl_3$ (150mL) was added and the mixture was filtrated, washed with $CHCl_3$, and concentrated under reduced pressure to provide 11.04g of the compound of formula **QC1** as a pale green solid (yield > 99.5%). The identity of the compound of formula **QC1** was confirmed using ^1H NMR and LC/MS.

Under a nitrogen atmosphere, to a solution of the compound of formula **QC1** (11.04 g, 31.2mmol) in toluene (220mL) at a temperature of about 25°C was added diethyl 2-oxomalonate (6.02mL, 37.5mmol) and AcOH (2.143mL, 37.5). After the addition, the resulting reaction mixture was heated to a temperature of 130°C and stirred for 1h. Thereafter, the reaction mixture was cooled to a temperature of about 25°C and concentrated under reduced pressure to provide a sticky oil. The oil was diluted with saturated aqueous $NaHCO_3$, extracted twice with $CHCl_3$ (600mL for each extraction), dried (Na_2SO_4), and concentrated under reduced pressure to provide an orange solid. The solid was sonicated using 4:1 n-hexane:Et_2O, collected by filtration, and dried under reduced pressure at 65°C for 8h to provide a first portion of the compound of formula **QC2** as a pale yellow solid. The remaining filtrate was chromatographed with a silica gel column eluted with a gradient of from 100%:0% $CHCl_3$:MeOH to 95%:5% $CHCl_3$:MeOH to provide a second portion of the compound of formula **QC2** as a pale yellow solid; a total of 9.83g was obtained (combined yield 67%). The identity of the compound of formula **QC2** was confirmed using ^1H NMR and LC/MS.

Thereafter, Substituted-Quinoxaline-Type Bridged-Piperidine Compound **362** was prepared from the compound of formula **QC2** as described in Example 1. The identity of Substituted-Quinoxaline-Type Bridged-Piperidine Compound **362** was confirmed using ^1H NMR and LC/MS.

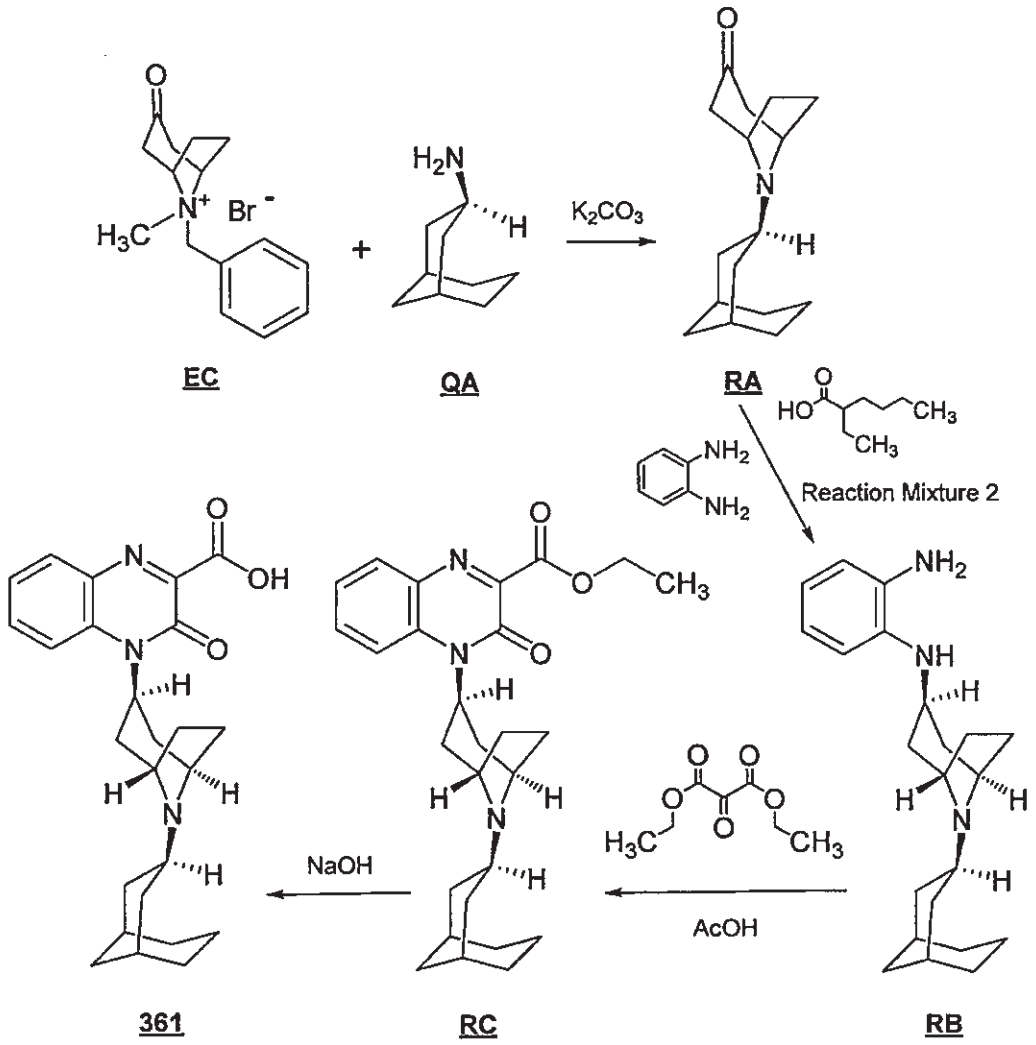
5.4 Example 4



EA **EB** **EC**

The compound of formula **EB** (6.5g, 38mmol) was added to a mixture of the compound of formula **EA**, 8-methyl-8-azabicyclo[3.2.1]octan-3-one (5g, 36mmol, Sigma-Aldrich), in acetone

(100mL) over 30 min at a temperature of about 25°C. The resulting reaction mixture was stirred at a temperature of about 25°C for 1h then at 38°C for 2h. Thereafter, the mixture was cooled to a temperature of about 25°C, filtered, and washed twice with hexanes (10mL for each wash) to provide 10g of the compound of formula EC, 8-benzyl-8-methyl-3-oxo-8-azoniabicyclo[3.2.1]octane bromide, as white solid (yield 85%).



To a mixture of the compound of formula QA (2270mg, 16.30mmol), K_2CO_3 (225.3mg, 1.63mmol), EtOH (20mL), and water (5mL) at a temperature of about 25°C was added dropwise a mixture of the compound of formula EC (5058mg, 16.30mmol), EtOH (20mL), and water (27mL). After the addition, the resulting reaction mixture was heated to a temperature of 90°C and stirred for 4h. Thereafter, the reaction mixture was cooled to a temperature of about 25°C, diluted with saturated aqueous $NaHCO_3$, then extracted twice with EtOAc:H_2O (100mL for each extraction). The organic portions were combined, dried (Na_2SO_4), and concentrated under reduced pressure to provide an oil. The oil was chromatographed with a silica gel column eluted with a gradient of

from 20%:80% EtOAc:n-hexane to 80%:20% EtOAc:n-hexane to provide 2030mg of the compound of formula **RA** as a colorless solid (yield 50%).

The identity of the compound of formula **RA**, 8-((*exo*)-bicyclo[3.3.1]nonan-3-yl)-8-azabicyclo[3.2.1]octan-3-one, was confirmed using ^{1}H NMR and LC/MS.

Compound **RA**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 1.79 (m, 12H), 2.26 (m, 8H), 2.87 (d, J=13.64Hz, 2H), 3.52 (td, J=11.12, 5.56Hz, 1H), 3.99 (s, 2H); LC/MS: *m/z*=248.5 $[M+H]^+$ (Calc: 247).

Under a nitrogen atmosphere, to a solution of the compound of formula **RA** (2029mg, 8.20mmol) in CH_2Cl_2 (25mL) at a temperature of about 25°C was added 1,2-phenylenediamine (2661mg, 24.61mmol) and 2-ethylhexanoic acid (1.971mL, 12.30mmol). The mixture was stirred at a temperature of about 25°C for 30min to provide reaction mixture 1.

Under a nitrogen atmosphere, to a solution of sodium tetrahydroborate (1241mg, 32.8mmol) in CH_2Cl_2 (17mL) at a temperature of about 25°C was added 2-ethylhexanoic acid (18.40mL, 115mmol). The mixture was stirred at a temperature of about 25°C for 30min to provide reaction mixture 2.

Under a nitrogen atmosphere, to reaction mixture 1 at 0°C was added reaction mixture 2 dropwise over a 15min period. After the addition, the resulting reaction mixture was heated to a temperature of about 25°C and stirred for 30min. Thereafter, the reaction mixture was heated to a temperature of 60°C and stirred for 16h. After cooling the reaction mixture to a temperature of about 25°C, saturated aqueous $NaHCO_3$ (20mL) was added, the mixture stirred for 10min, then extracted twice with 1M aqueous K_2CO_3/EtOAc (150mL for each extraction). The organic portions were combined, dried (Na_2SO_4), and concentrated under reduced pressure to provide a yellow oil. The oil was chromatographed with a silica gel column eluted with a gradient of from 97%:3% $CHCl_3$:(10% NH_3 in MeOH) to 80%:20% $CHCl_3$:(10% NH_3 in MeOH) to provide 874mg of the compound of formula **RB** as a pale yellow amorphous solid (yield 31%).

The identity of the compound of formula **RB**, N^1-((*endo*)-8-((*exo*)-bicyclo[3.3.1]nonan-3-yl)-8-azabicyclo[3.2.1]octan-3-yl)benzene-1,2-diamine, was confirmed using ^{1}H NMR and LC/MS.

Compound **RB**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 0.91 (m, 3H), 1.26-2.10 (m, 20H), 2.35 (m, 2H), 3.28-3.33 (m, 1H), 3.69 (m, 3H), 6.57 (d, J=7.58Hz, 1H), 6.75 (m, 3H); LC/MS: *m/z*=340.6 $[M+H]^+$ (Calc: 339).

Under a nitrogen atmosphere, to a solution of the compound of formula **RB** (870mg, 2.56mmol) in xylene (15mL) at a temperature of about 25°C was added diethyl 2-oxomalonate (0.494mL, 3.07mmol) and AcOH (0.176mL, 3.07mmol). After the addition, the resulting reaction mixture was heated to a temperature of 130°C and stirred for 1h. Thereafter, the reaction mixture

was cooled to a temperature of about 25°C, diluted with saturated aqueous $NaHCO_3$, extracted twice with EtOAc (100mL for each extraction), dried (Na_2SO_4), and concentrated under reduced pressure to provide an orange oil. The oil was chromatographed with an amino-silica gel column (Yamazen Corp. W091-01) eluted with a gradient of from 5%:95% EtOAc:n-hexane to 30%:70% EtOAc:n-hexane to provide a pale yellow solid. The solid was triturated with 1:4 Et_2O:n-hexane and dried under reduced pressure at 70°C to provide 343mg of the compound of formula **RC** as a colorless solid (yield 30%).

The identity of the compound of formula **RC**, ethyl 4-((*endo*)-8-((*exo*)-bicyclo[3.3.1]nonan-3-yl)-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

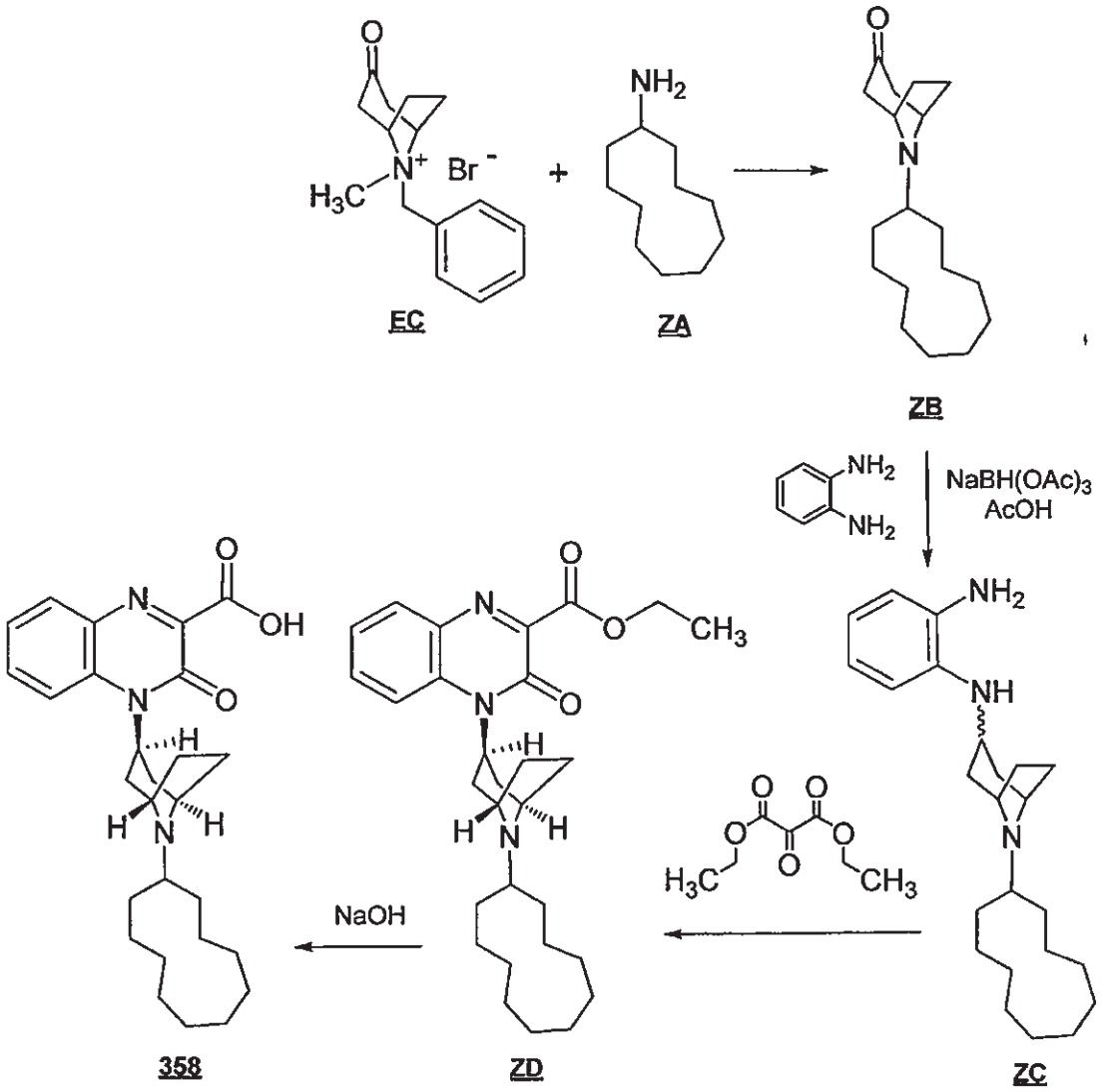
Compound **RC**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 0.83-0.88 (m, 1H), 1.26 (dd, J=33.09, 17.94Hz, 3H), 1.51 (m, 11H), 1.91 (m, 8H), 2.20 (s, 3H), 2.79 (dt, J=11.62Hz, 3.66Hz, 1H), 3.70 (s, 2H), 4.50 (q, J=7.07Hz, 2H), 5.20 (br, 1H), 7.34 (t, J=7.07Hz, 1H), 7.61 (q, J=7.92Hz, 2H), 7.91 (d, J=7.58Hz, 1H); LC/MS: *m/z*=450.1 $[M+H]^+$ (Calc: 449).

To a solution of the compound of formula **RC** (343mg, 0.763mmol) in EtOH (10mL) at a temperature of about 25°C was added 2N aqueous NaOH (1.144mL, 2.289mmol). The resulting reaction mixture was stirred at a temperature of about 25°C for 1h. Thereafter, the reaction mixture was concentrated under reduced pressure to provide a residue. The residue was diluted with water (2mL) to form a pale yellow solution, neutralized with 2N aqueous HCl (1.144mL), and sonicated to provide a white precipitate. The precipitate was collected by filtration, washed with water, and dried at 75°C for 8h under reduced pressure to provide 312mg of Substituted-Quinoxaline-Type Bridged-Piperidine Compound **361** as a colorless solid (yield 97%).

The identity of Substituted-Quinoxaline-Type Bridged-Piperidine Compound **361**, 4-((*endo*)-8-((*exo*)-bicyclo[3.3.1]nonan-3-yl)-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Bridged-Piperidine Compound **361**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 0.86 (m, 2H), 1.64 (m, 6H), 1.89 (m, 1H), 2.03 (dq, J=9.09, 2.44Hz, 2H), 2.42 (m, 9H), 3.01 (m, 2H), 3.49 (s, 1H), 4.26 (d, J=1.01Hz, 2H), 6.55 (s, 1H), 7.55 (t, J=7.33Hz, 1H), 7.92 (dd, J=9.85, 5.81Hz, 1H), 8.18 (d, J=7.58Hz, 1H), 8.40 (d, J=8.59Hz, 1H), 11.41 (s, 1H); LC/MS (100%, t_r=1.38min): *m/z*=422.5 $[M+H]^+$ (Calc: 421.5).

5.5 Example 5



The compound of formula **EC** was mixed with 2:1 EtOH:H_2O. Over 30min, this mixture was added to a mixture of the compound of formula **ZA** (cycloundecanamine, Sigma-Aldrich) and K_2CO_3 in EtOH at 70°C. After 3h at 70°C, the reaction mixture was cooled to a temperature of about 25°C and concentrated under reduced pressure. The residue was treated with water and extracted three times with $CHCl_3$. The combined organic portions were washed with brine and concentrated under reduced pressure to provide the compound of formula **ZB**.

The identity of the compound of formula **ZB**, 8-cycloundecyl-8-azabicyclo[3.2.1]octan-3-one, was confirmed using ^1H NMR.

Compound **ZB**: ^1H NMR: δ_H (400MHz, $CDCl_3$): 1.46-1.77 (m, 22H), 1.97 (m, 2H), 2.14 (d, J=16.22Hz, 2H), 2.64 (d, J=16.22Hz, 2H), 2.73 (m, 1H), 3.77 (s, 2H).

Sodium triacetoxyborohydride (Sigma-Aldrich) was added to a mixture of the compound of formula **ZB** and 1,2-phenylenediamine in CH_2Cl_2 at a temperature of about 25°C. Thereafter, acetic acid was added. The resulting reaction mixture was stirred at a temperature of about 25°C for about 16h. Thereafter, MeOH and water were added and the mixture was neutralized with 28% aqueous ammonia to adjust the pH to about 8. The organic portion was separated, washed with brine, concentrated under reduced pressure, and chromatographed with a silica gel column eluted with 10:1:1 EtOAc:MeOH:TEA to provide a mixture of the *endo* and *exo* isomers of the compound of formula **ZC**.

The identity of the compound of formula **ZC**, N^1-(8-cycloundecyl-8-azabicyclo[3.2.1]octan-3-yl)benzene-1,2-diamine, was confirmed using ^{1}H NMR and LC/MS.

Compound **ZC**: ^{1}H NMR: δ_H ($CDCl_3$): 1.57 (m, 22H), 2.00 (m, 4H), 2.23 (m, 2H), 2.47 (m, 1H), 3.33 (m, 2H), 3.48 (m, 3H), 3.68 (m, 1H), 6.57 (d, J=7.72Hz, 1H), 6.69 (t, J=7.72Hz, 1H), 6.76 (d, J=7.55Hz, 1H), 6.84 (t, J=7.55Hz, 1H); LC/MS: *m/z*=370 $[M+H]^+$ (Calc: 369.6).

Diethyl 2-oxomalonate was added dropwise to a suspension of the compound of formula **ZC** in toluene at 25°C. The resulting reaction mixture was stirred at 130°C for 4hr. After cooling to a temperature of about 25°C and concentrating under reduced pressure, an oil was obtained. The oil was chromatographed with a silica gel column eluted with a gradient of from 99%:1% $CHCl_3$:MeOH to 95%:5% $CHCl_3$:MeOH to provide an amorphous solid. The solid was chromatographed with a silica gel column eluted with a gradient of from 95%:5% EtOAc:MeOH to 90%:10% EtOAc:MeOH to provide the compound of formula **ZD**.

The identity of the compound of formula **ZD**, ethyl 4-((*endo*)-8-cycloundecyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

Compound **ZD**: ^{1}H NMR: δ_H ($CDCl_3$): 1.30-1.70 (m, 24H), 1.83 (m, 2H), 2.00 (m, 2H), 2.25 (m, 5H,), 3.66 (m, 2H), 4.50 (d, J=7.14Hz, 2H), 5.20 (br, 1H), 7.36 (t, J=7.60Hz, 1H), 7.56 (d, J=7.60Hz, 1H), 7.60 (t, J=7.60Hz, 1H), 7.91 (d, J=7.60Hz, 1H); LC/MS: *m/z*=480 $[M+H]^+$ (Calc: 479.6).

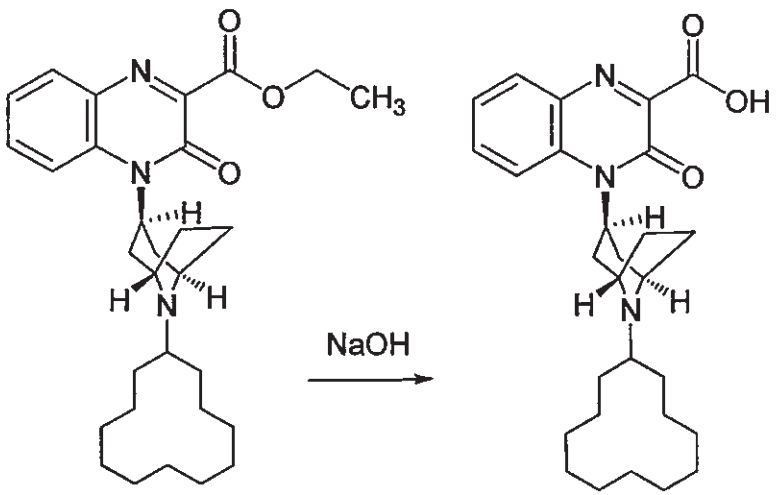
To a mixture of the compound of formula **ZD** in MeOH at a temperature of about 25°C was added 2N aqueous NaOH. The resulting reaction mixture was stirred for 2h at a temperature of about 25°C. After concentration under reduced pressure, the mixture was diluted with water then extracted with EtOAc. The aqueous portion was neutralized by adding a first treatment of 2N aqueous HCl at a temperature of 0°C. Thereafter, the mixture was extracted twice with $CHCl_3$. The organic portions were combined, dried ($MgSO_4$), filtrated, and concentrated under reduced pressure to provide Substituted-Quinoxaline-Type Bridged-Piperidine Compound **358**.

The identity of Substituted-Quinoxaline-Type Bridged-Piperidine Compound **358**, 4-((*endo*)-8-cycloundecyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Bridged-Piperidine Compound **358**: ^{1}H NMR: δ_H ($CDCl_3$): 1.30-1.60 (m, 14H), 1.75 (m, 2H), 2.13 (m, 6H), 2.39 (m, 4H), 2.61 (m, 1H), 3.04 (m, 2H), 4.12 (m, 2H), 5.83 (m, 1H), 7.25 (m, 1H), 7.44 (m, 1H), 7.85-7.94 (m, 2H); LC/MS (99%, t_r=2.06min): *m/z*=452 $[M+H]^+$ (Calc: 451.6).

5.6 Example 6

In a manner similar to Example 5, the compound of formula **SA** and Substituted-Quinoxaline-Type Bridged-Piperidine Compound **356** were prepared from the compound of formula **EC** by using cyclododecanamine (Sigma-Aldrich) in place of the compound of formula **ZD**.



SA **356**

The identity of the compound of formula **SA**, ethyl 4-((*endo*)-8-cyclododecyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

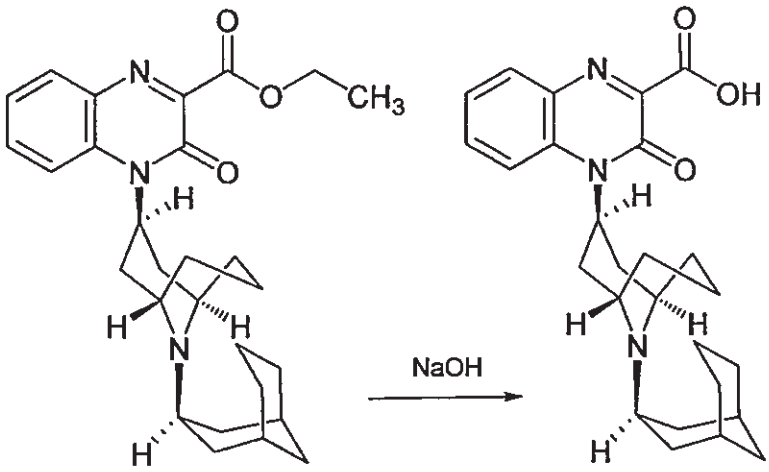
Compound **SA**: ^{1}H NMR: δ_H ($CDCl_3$): 1.35 (m, 25.0H), 1.82 (m, 2.0H), 2.02 (m, 2.0H), 2.26 (m, 5.0H), 3.68 (m, 2.0H), 4.49 (q, J = 7.10 Hz, 2.0H), 5.20 (br, 1.0H), 7.34 (t, J = 7.60 Hz, 1.0H), 7.54 (d, J = 7.60 Hz, 1.0H), 7.62 (t, J = 7.60 Hz, 1.0H), 7.91 (d, J = 7.60 Hz, 1.0H); LC/MS: *m/z*=494 $[M+H]^+$ (Calc: 493.6).

The identity of Substituted-Quinoxaline-Type Bridged-Piperidine Compound **356**, 4-((*endo*)-8-cyclododecyl-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Bridged-Piperidine Compound **356**: ^{1}H NMR: δ_H ($CDCl_3$): 1.42 (m, 16.0H), 1.60-2.60 (m, 12.0H), 2.72 (s, 1.0H), 3.06 (m, 2.0H), 4.16 (s, 2.0H), 6.00 (br, 1.0H), 7.32 (t, J = 7.35 Hz, 1.0H), 7.60 (m, 1.0H), 7.93 (d, J = 8.11 Hz, 1.0H).8.10 (m, 1.0H); LC/MS (100%, t_r=2.20min): *m/z*=466 $[M+H]^+$ (Calc: 465.6).

5.7 Example 7

In a manner similar to Example 1, the following Substituted-Quinoxaline-Type Bridged-Piperidine Compound was prepared from the compound of formula **LB**.



TA **369**

The compound of formula **TA** (yield 8% for three steps) and Substituted-Quinoxaline-Type Bridged-Piperidine Compound **369** (yield 91%) were prepared from the compound of formula **LB** by using (*endo*)-bicyclo[3.3.1]nonan-3-amine (**QI**) in place of the compound of formula **QA**.

The identity of the compound of formula **TA**, ethyl 4-((*endo*)-9-((*endo*)-bicyclo[3.3.1]nonan-3-yl)-9-azabicyclo[3.3.1]nonan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

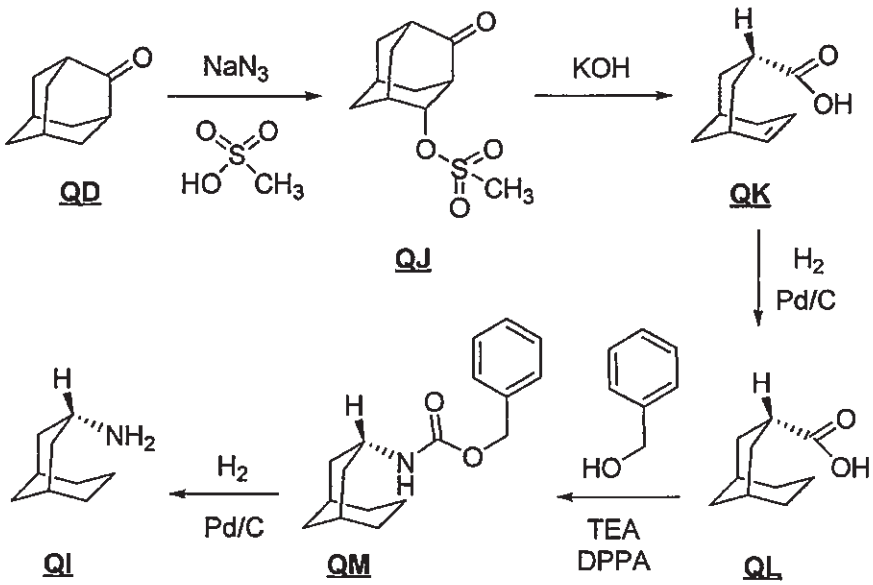
Compound **TA**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 0.98-1.12 (m, 5H), 1.26 (s, 1H), 1.43 (m, 7H), 1.57 (m, 1H), 1.75-1.85 (m, 5H), 2.10 (m, 5H), 2.40-2.45 (m, 1H), 2.72 (br, 2H), 3.00-3.07 (m, 1H), 3.53 (d, J=10.11Hz, 2H), 4.51 (q, J=7.07Hz, 2H), 5.20 (br, 1H), 7.36 (t, J=3.54Hz, 1H), 7.65 (s, 2H), 7.93 (d, J=8.08Hz, 1H); LC/MS: *m/z*=464.1 $[M+H]^+$ (Calc: 463).

The identity of Substituted-Quinoxaline-Type Bridged-Piperidine Compound **369**, 4-((*endo*)-9-((*endo*)-bicyclo[3.3.1]nonan-3-yl)-9-azabicyclo[3.3.1]nonan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Bridged-Piperidine Compound **369**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 0.84-0.89 (m, 1H), 1.27 (m, 4H), 1.40-1.52 (m, 2H), 1.66 (m, 5H), 1.85 (m,

1H), 2.11 (m, 2H), 2.28 (s, 4H), 2.50 (m, 2H), 2.76 (m, 1H), 3.00 (t, J=12.63Hz, 2H), 3.69-3.74 (m, 1H), 4.16 (d, J=10.11Hz, 2H), 6.78 (s, 1H), 7.56 (t, J=7.58Hz, 1H), 7.93 (t, J=7.83Hz, 1H), 8.19 (d, J=8.08Hz, 1H), 9.07 (t, J=7.58Hz, 1H), 11.08 (s, 1H); LC/MS (100%, t_r=1.55min): *m/z*=436.2 $[M+H]^+$ (Calc: 436).

The compound of formula **QI** was prepared as follows.



Under a nitrogen atmosphere, to a solution of the compound of formula **QD** (6.0g, 39.9mmol) in methane sulfonic acid (33.7mL, 519mmol) at a temperature of 20°C was added sodium azide (2.726g, 41.9mmol) portionwise over 2.5h. After the addition, the resulting reaction mixture was stirred for 3 days at 20°C. Thereafter, ice-water (300mL) was poured into the reaction mixture to provide a white precipitate that was collected by filtration, washed with water, and dried at 40°C for 6h under reduced pressure to provide 5.63g of the compound of formula **QJ** as a colorless solid with a melting point of 69-72°C (yield 58%).

The identity of the compound of formula **QJ**, methane sulfonic acid 4-oxo-adamantan-2-yl ester, was confirmed using ^{1}H NMR.

Compound **QJ**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 1.75-2.12 (m, 9H), 2.31 (m, 1H), 2.41-2.50 (m, 2H), 2.58 (s, 1H), 2.88 (s, 1H), 3.05 (d, J=6.59Hz, 3H), 4.80 (t, J=3.55Hz, 1H).

To a solution of the compound of formula **QJ** (5.63g, 23.04mmol) in EtOH (100mL) at a temperature of about 25°C was added a KOH (8.469g, 151mmol) in water (67mL) solution. After the addition, the resulting reaction mixture was heated to a temperature of 110°C and stirred for 12h. Thereafter, the reaction mixture was cooled to a temperature of about 25°C, 10% aqueous HCl was added such that the pH was within 3 to 4, and a colorless precipitate formed. The precipitate was collected by filtration, washed with water, concentrated under reduce pressure, and dried at

50°C for 8h under reduced pressure to provide 3.61g of the compound of formula **QK** as a colorless solid with a melting point of 189-192°C (yield 94%).

The identity of the compound of formula **QK**, (*endo*)-bicyclo[3.3.1]non-6-ene-3-carboxylic acid, was confirmed using ^{1}H NMR.

Compound **QK**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 1.64 (m, 4H), 2.07-2.42 (m, 6H), 2.58 (t, J=6.32Hz, 1H), 5.57-5.68 (m, 2H).

In a manner similar to the preparation of the compound of formula **QF** above, the compound of formula **QL** was prepared from the compound of formula **QK** (yield 99%).

The identity of the compound of formula **QL**, (*endo*)-bicyclo[3.3.1]nonane-3-carboxylic acid, was confirmed using ^{1}H NMR.

Compound **QL**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 1.17 (d, J=13.18Hz, 1H), 1.37-1.82 (m, 10H), 2.12 (m, 4H), 2.51-2.60 (m, 1H).

In a manner similar to the preparation of the compound of formula **QH** above, the compound of formula **N** was prepared from the compound of formula **QL** (yield 90%).

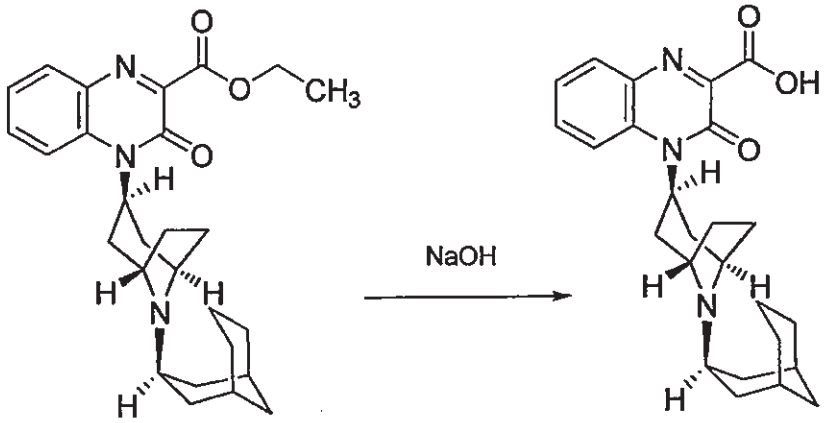
The identity of the compound of formula **QM**, benzyl (*endo*)-bicyclo[3.3.1]nonan-3-ylcarbamate, was confirmed using ^{1}H NMR and LC/MS.

Compound **QM**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 1.31 (m, 2H), 1.44-1.76 (m, 9H), 2.04 (s, 2H), 2.09 (s, 2H), 4.31-4.40 (m, 2H), 5.08 (s, 2H), 7.28-7.39 (m, 5H); LC/MS: *m/z*=274.2 $[M+H]^+$ (Calc: 273).

Under a hydrogen atmosphere, a mixture of the compound of formula **QM** (4.11g, 15.03mmol), 10% palladium on carbon (0.64g, 0.601mmol), and EtOH (45mL) was stirred at a temperature of about 25°C for 3h. After filtering off the Pd/C and washing with EtOH, the mixture was concentrated under reduced pressure to a volume of 10mL. The EtOH solution contained 2.093g (15.03mmol) of the compound of formula **QI**.

5.8 Example 8

In a manner similar to Example 4, the compound of formula **UA** (yield 4% for three steps) and Substituted-Quinoxaline-Type Bridged-Piperidine Compound **360** (yield 87%) were prepared from the compound of formula **EC** by using the compound of formula **QI** in place of the compound of formula **QA**.



UA 360

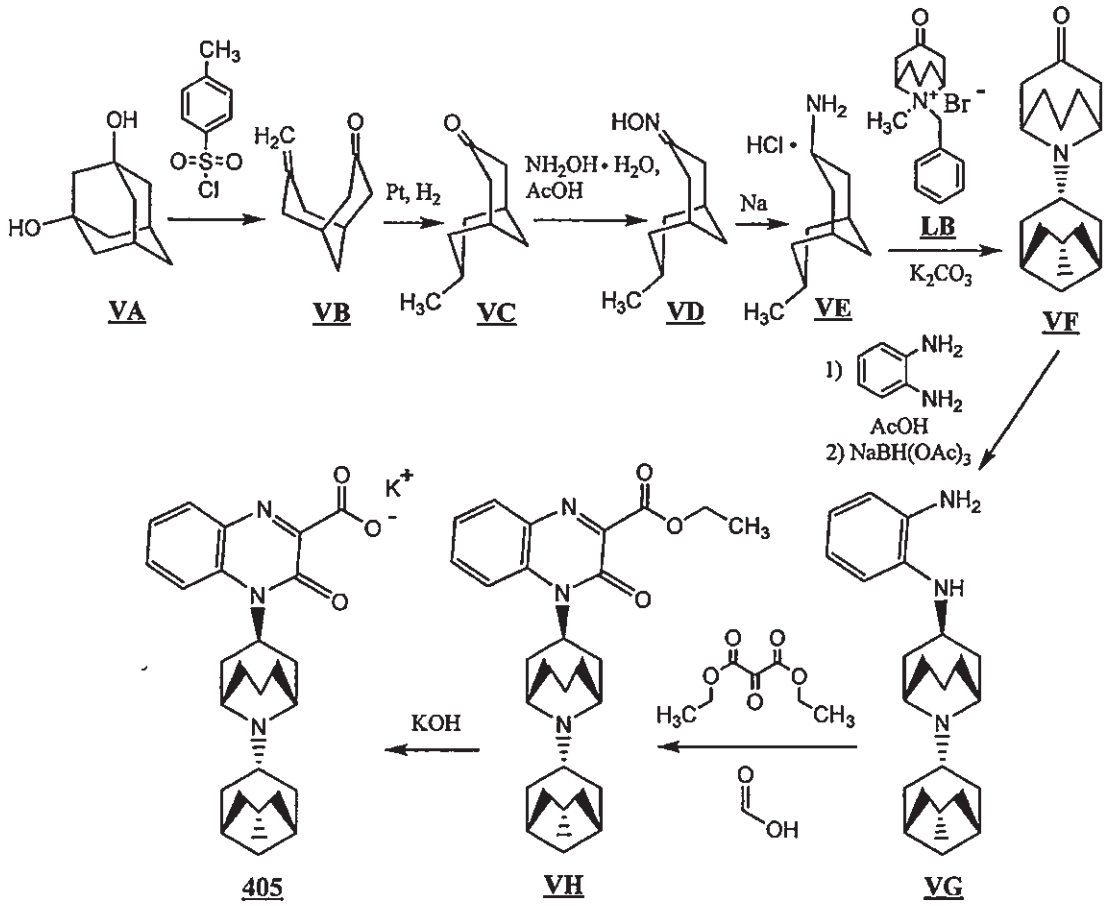
The identity of the compound of formula UA, ethyl 4-((*endo*)-8-((*endo*)-bicyclo[3.3.1]nonan-3-yl)-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^{1}H NMR and LC/MS.

Compound UA: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 0.86 (dq, J=10.11, 2.69Hz, 1H), 1.07 (m, 3H), 1.21-1.45 (m, 10H), 1.65-2.37 (m, 15H), 3.67 (t, J=2.53Hz, 2H), 4.50 (q, J=7.07Hz, 2H), 5.18 (br, 1H), 7.35 (t, J=7.33Hz, 1H), 7.60 (t, J=9.60Hz, 2H), 7.91 (d, J=8.08Hz, 1H); LC/MS: *m/z*=450.2 $[M+H]^+$ (Calc: 449).

The identity of Substituted-Quinoxaline-Type Bridged-Piperidine Compound 360, 4-((*endo*)-8-((*endo*)-bicyclo[3.3.1]nonan-3-yl)-8-azabicyclo[3.2.1]octan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Bridged-Piperidine Compound 360: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 0.84-0.88 (m, 4H), 1.38-1.46 (m, 1H), 1.54-1.65 (m, 3H), 2.27 (m, 6H), 2.46 (dt, J=12.80Hz, 4.93Hz, 3H), 2.95 (br, 3H), 4.25 (s, 2H), 6.61 (s, 1H), 7.51 (d, J=8.08Hz, 1H), 7.88 (dd, J=9.60, 5.05Hz, 1H), 8.14 (d, J=8.59Hz, 1H), 8.44 (d, J=4.04Hz, 1H), 11.55 (s, 1H); LC/MS (100%, t_r=1.48min): *m/z*=422.2 $[M+H]^+$ (Calc: 421.5).

5.9 Example 9



To a solution of the compound of formula **VA** (1,3-dihydroxyadamantane, 50.0g, 297.3mmol, Sigma-Aldrich) in pyridine (150mL) at a temperature of about 25°C was added 4-methylbenzene-1-sulfonyl chloride (62.4g, 327.0mmol, Sigma-Aldrich). The resulting reaction mixture was heated at 70°C for 6h. After cooling to a temperature of about 25°C, the mixture was poured into saturated aqueous brine solution (1L) and that mixture was extracted twice with 1:1 Et_2O:hexanes (1L for each extraction). The organic portions were combined, washed with brine (1L), dried ($MgSO_4$), and concentrated to dryness under reduced pressure to provide a pale yellow solid. The residue was chromatographed with a silica gel column eluted with 100:10:1 hexanes:EtOAc:TEA to provide 29.0g of the compound of formula **VB** as a white solid (yield 65%).

The identity of the compound of formula **VB**, 7-methylenebicyclo[3.3.1]nonan-3-one, was confirmed using ^{1}H NMR.

Compound **VB**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 4.70 (2H, s), 2.40-2.13 (12H, m), 1.87 (2H, m).

Under a hydrogen atmosphere, to a solution of the compound of formula **VB** (5.0g, 38.29mmol) in cyclohexane (100mL) at a temperature of about 25°C was added platinum black (250mg, Sigma-Aldrich). The resulting reaction mixture was stirred vigorously at a temperature of about 25°C for 24h. The mixture was filtered and the filtrate evaporated to dryness under reduced pressure to provide the compound of formula **VC**, 7-methylbicyclo[3.3.1]nonan-3-one, as a pale yellow oil.

To a solution of the compound of formula **VC** from the previous step in acetic acid (20mL) at a temperature of about 25°C was added 50% aqueous hydroxylamine (5mL). The resulting reaction mixture was heated at 70°C for 2h. Thereafter, the mixture was poured into 8% aqueous sodium bicarbonate solution (250mL), extracted twice with EtOAc (250mL for each extraction), dried ($MgSO_4$), and evaporated to dryness under reduced pressure to provide a residue. The residue was recrystallized from hexanes (50mL) at -10°C to provide 1.90g of a first portion of the compound of formula **VD**. The filtrate was concentrated to dryness under reduced pressure and chromatographed with a silica gel column eluted with 1:1 hexanes:EtOAc to provide a 2.15g second portion of the compound of formula **VD**.

The identity of the compound of formula **VD**, 7-methylbicyclo[3.3.1]nonan-3-one oxime, was confirmed using ^{1}H NMR and TLC.

Compound **VD**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 7.8 (1H, bs), 3.2 (1H, d, J=12Hz), 2.40-2.10 (4H, m), 2.00-1.73 (4H, m), 1.55 (1H, m), 1.32 (1H, d, J=12Hz), 0.80 (4H, m), 0.62 (2H, m); TLC (SiO_2, 1:10 EtOAc:hexanes) R_f=0.20 (visualized with molybdophosphoric acid).

Under a nitrogen atmosphere and with stirring, to dry toluene (25mL) was added small pieces of sodium (3.0g, 130.4mmol). The resulting suspension was heated to reflux and to it was added dropwise a mixture of the compound of formula **VD** (2.15g, 12.86mmol), toluene (25mL), and isopropanol (10mL). The resulting reaction mixture was stirred under reflux for 3h. The mixture was cooled to a temperature of about 25°C, quenched with MeOH (10mL) followed by water (5mL), and the resulting mixture stirred for 15min. The mixture was partitioned between 1M aqueous KOH (200mL) and Et_2O (200mL). The organic portion was separated, dried ($MgSO_4$), and filtered. The filtrate was treated with 2M HCl in Et_2O (20mL) and the mixture filtered to provide a 1.12g first portion of the compound of formula **VE** as a white crystalline solid. The filtrate was evaporated to dryness under reduced pressure, Et_2O (100mL) was added, and the mixture filtered to provide a 0.44g second portion of the compound of formula **VE**; a total of 1.56g was obtained (combined yield 63%).

The identity of the compound of formula **VE**, (*exo, endo*)-7-methylbicyclo[3.3.1]nonan-3-amine hydrochloride, was confirmed using ^{1}H NMR.

Compound **VE**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 8.20 (3H, bs),3.43 (1H, m), 2.10 (2H, m), 1.85 (4H, m), 1.65-1.43 (5H, m), 1.00 (1H, d, J=12Hz), 0.75 (3H, d, J=6Hz), 0.65 (2H, dt, J=12Hz, 2Hz).

The compound of formula **VE** (1.56g, 8.22mmol), the compound of formula **LB** (3.20g, 9.87mmol), and K_2CO_3 (1.25g, 9.04mmol) were suspended in a mixture of EtOH (10mL) and water (6mL). The resulting reaction mixture was heated with stirring under reflux for 6h, then allowed to cool to a temperature of about 25°C over 18h. The mixture was filtered to provide 2.00g of the compound of formula **VF** as long white needles (yield 87%). It should be noted that in the above reaction scheme drawing for the compound of formula **VF** and the compounds prepared from it, for simplicity the "CH_3" notation for the 7-methyl substituent has been omitted.

The identity of the compound of formula **VF**, (*exo, endo*)-9-(7-methylbicyclo[3.3.1]nonan-3-yl)-9-azabicyclo[3.3.1]nonan-3-one, was confirmed using ^{1}H NMR.

Compound **VF**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 3.70 (2H, m), 3.05 (1H, m), 3.66 (2H, m), 3.04 (1H, m), 2.62 (2H, dd, J=16.7, 6.7Hz), 2.22 (4H, m), 2.03-1.45 (13H, m), 1.26 (2H, dt, J=13.3Hz, 3.3Hz), 1.06 (1H, dt, J=13.3Hz, 3.3Hz), 0.86 (3H, d, J=6.7Hz), 0.79 (2H, t, J= 13.3Hz).

The compound of formula **VF** (1.00g, 3.63mmol) and 1,2-phenylenediamine (0.471g, 4.36mmol) were dissolved in DME (2.5mL). At a temperature of about 25°C, acetic acid (1mL) was added and the resulting reaction mixture stirred for 24h. Then, sodium triacetoxyborohydride (2.69g, 12.71mmol) was added and the resulting reaction mixture stirred for 6h at a temperature of about 25°C. Thereafter, the mixture was quenched with water (5mL) then partitioned between $CHCl_3$ (250mL) and water (250mL). The organic portion was separated, washed with 10% aqueous acetic acid (250mL), dried ($MgSO_4$), and evaporated to dryness under reduced pressure to provide 1.20g of the compound of formula **VG**, (*exo, endo, endo*)-*N*^{1}-(7-methylbicyclo[3.3.1]nonan-3-yl)-9-azabicyclo[3.3.1]nonan-3-yl)-benzene-1,2-diamine, as an orange gum which was used immediately in the following step.

Under a nitrogen atmosphere, to a solution of the compound of formula **VG** (1.10g, 2.99mmol) in toluene (10mL) at a temperature of about 25°C was added formic acid (0.34mL, 8.97mmol) followed by diethyl 2-oxomalonate (0.55mL, 3.59mmol). After the addition, the resulting reaction mixture was heated to a temperature of 110°C and stirred for 1h. Thereafter, the reaction mixture was cooled to a temperature of about 25°C and EtOAc (100mL) was added. That mixture was washed with 1M aqueous Na_2CO_3 solution (100mL), dried ($MgSO_4$), and evaporated to dryness under reduced pressure to provide an orange gum. The orange gum was chromatographed with a silica gel column eluted with 900:100:20:1 hexanes:EtOAc:MeOH:ammonia to provide a yellow gum. The yellow gum was recrystallized from 1:1 Et_2O:hexanes (10mL) to provide 400mg of the compound of formula **VH** as a pale yellow

solid. By mass spectrometry analysis, this product was found to contain about 10% of an impurity of $[M+H]^+$ equal to 451, which may have been the free carboxylic acid of the compound of formula **VH**. Therefore, the solid was dissolved in hot MeOH (25mL), cooled to 0°C with stirring over 1h, and filtered to provide 313mg of relatively pure compound of formula **VH** as a white solid (yield 22% for two steps).

The identity of the compound of formula **VH**, ethyl (*exo, endo, endo*)-4-(9-(7-methylbicyclo[3.3.1]nonan-3-yl)-9-azabicyclo[3.3.1]nonan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylate, was confirmed using ^{1}H NMR and TLC.

Compound **VH**: ^{1}H NMR: δ_H (400MHz, $CDCl_3$): 7.88 (1H, d, J=8Hz), 7.55 (2H, m), 7.30 (1H, t, J=8Hz), 5.05 (1H, bs), 4.47 (2H, q, J=10Hz), 3.43 (2H, m), 3.05 (1H, m), 2.65 (2H, m), 2.37 (1H, m), 2.13 (2H, m), 1.96-1.50 (12H, m), 1.38 (3H, t, J=10Hz), 1.10 (4H, m), 0.95 (1H, m), 0.80 (5H, m); TLC (SiO_2, 900:100:20:1 hexanes:EtOAc:MeOH:ammonia) R_f=0.2 (ultraviolet detection, potassium iodoplatinate).

To a solution of the compound of formula **VH** (300mg, 0.628mmol) in THF (5mL) at a temperature of about 25°C was added a solution of KOH (106mg) in water (1mL). The resulting reaction mixture was stirred at a temperature of about 25°C for 3h. Thereafter, the reaction mixture was concentrated to dryness under reduced pressure to provide a residue. The residue was diluted with water (15mL) and the resulting mixture was filtered, washed with water (5mL), and dried at 50°C for 48h under reduced pressure to provide 300mg of the potassium salt of Substituted-Quinoxaline-Type Bridged-Piperidine Compound **405** as a white solid (yield > 99.5%).

The identity of Substituted-Quinoxaline-Type Bridged-Piperidine Compound **405**, (*exo, endo, endo*)-4-(9-(7-methylbicyclo[3.3.1]nonan-3-yl)-9-azabicyclo[3.3.1]nonan-3-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid potassium salt, was confirmed using ^{1}H NMR and LC/MS.

Substituted-Quinoxaline-Type Bridged-Piperidine Compound **405**: ^{1}H NMR: δ_H (400MHz, DMSO-d_6): 7.70 (1H, d, J=10Hz), 7.50 (2H, m), 7.28 (1H, m), 4.90 (1H, m), 3.46 (2H, m), 3.08 (1H, m), 2.38 (1H, m), 2.15 (2H, m), 2.00-1.80 (6H, m), 1.75-1.50 (5H, m), 1.16 (4H, m), 1.00 (1H, m), 0.90 (5H, m); LC/MS (100%): *m/z*=450 $[M+H]^+$ (Calc: 451).

5.10 Example 10: *In vitro* ORL-1 Receptor Binding Assay

ORL-1 Receptor Binding Assay Procedures: Membranes from recombinant HEK-293 cells expressing the human opioid receptor-like receptor (ORL-1) (Receptor Biology) were prepared by lysing cells in ice-cold hypotonic buffer (2.5mM $MgCl_2$, 50mM HEPES, pH 7.4) (10mL/10 cm dish) followed by homogenization with a tissue grinder/Teflon pestle. Membranes were collected by centrifugation at 30,000 x g for 15min at 4°C and pellets resuspended in hypotonic buffer to a final concentration 1-3mg/mL. Protein concentrations were determined using

the BioRad protein assay reagent with bovine serum albumen as a standard. Aliquots of the ORL-1 receptor membranes were stored at -80°C.

Radioligand binding assays (screening and dose-displacement) used 0.1nM [^{3}H]-nociceptin (NEN; 87.7 Ci/mmole) with 10-20μg membrane protein in a final volume of 500μL binding buffer (10mM $MgCl_2$, 1mM EDTA, 5% DMSO, 50mM HEPES, pH 7.4). Non-specific binding was determined in the presence of 10nM unlabeled nociceptin (American Peptide Company). All reactions were performed in 96-deep well polypropylene plates for 1 h at about 25°C. Binding reactions were terminated by rapid filtration onto 96-well Unifilter GF/C filter plates (Packard) presoaked in 0.5% polyethylenimine (Sigma). Harvesting was performed using a 96-well tissue harvester (Packard) followed by three filtration washes with 500μL ice-cold binding buffer. Filter plates were subsequently dried at 50°C for 2-3 hours. Fifty μL/well scintillation cocktail (BetaScint; Wallac) was added and plates were counted in a Packard Top-Count for 1 min/well. The data from screening and dose-displacement experiments were analyzed using Microsoft Excel and the curve fitting functions in GraphPad PRISM™, v. 3.0, respectively, or an in-house function for one-site competition curve-fitting.

ORL-1 Receptor Binding Data: Typically, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a K_i (nM) of about 300 or less for binding to ORL-1 receptors. In one embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a K_i (nM) of about 100 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a K_i (nM) of about 35 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a K_i (nM) of about 20 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a K_i (nM) of about 15 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a K_i (nM) of about 10 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a K_i (nM) of about 4 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a K_i (nM) of about 1 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a K_i (nM) of about 0.4 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a K_i (nM) of about 0.1 or less.

5.11 Example 11: *In vitro* ORL-1 Receptor Functional Assay

ORL-1 Receptor [^{35}S]GTPγS Binding Assay Procedures: Membranes from recombinant HEK-293 cells expressing the human opioid receptor-like (ORL-1) (Receptor Biology) were prepared by lysing cells in ice-cold hypotonic buffer (2.5mM $MgCl_2$, 50mM

HEPES, pH 7.4) (10mL/10 cm dish) followed by homogenization with a tissue grinder/Teflon pestle. Membranes were collected by centrifugation at 30,000 x g for 15min at 4°C, and pellets resuspended in hypotonic buffer to a final concentration of 1-3mg/mL. Protein concentrations were determined using the BioRad protein assay reagent with bovine serum albumen as a standard. Aliquots of the ORL-1 receptor membranes were stored at -80°C.

Functional binding assays were conducted as follows. ORL-1 membrane solution was prepared by sequentially adding final concentrations of 0.066μg/μL ORL-1 membrane protein, 10μg/mL saponin, 3μM GDP and 0.20nM [35S]GTPγS to binding buffer (100mM NaCl, 10mM $MgCl_2$, 20mM HEPES, pH 7.4) on ice. The prepared membrane solution (190μL/well) was transferred to 96-shallow well polypropylene plates containing 10μL of 20x concentrated stock solutions of agonist/nociceptin prepared in DMSO. Plates were incubated for 30min at about 25°C with shaking. Reactions were terminated by rapid filtration onto 96-well Unifilter GF/B filter plates (Packard) using a 96-well tissue harvester (Packard) and followed by three filtration washes with 200μL ice-cold binding buffer (10mM NaH_2PO_4, 10mM Na_2HPO_4, pH 7.4). Filter plates were subsequently dried at 50°C for 2-3 hours. Fifty μL/well scintillation cocktail (BetaScint; Wallac) was added and plates were counted in Packard Top-Count for 1 min/well. Data are analyzed using the sigmoidal dose-response curve fitting functions in GraphPad PRISM v. 3.0, or an in-house function for non-linear, sigmoidal dose-response curve-fitting.

ORL-1 Receptor Functional Data: ORL-1 GTP EC_{50} is the concentration of a compound providing 50% of the maximal response for the compound at an ORL-1 receptor. Substituted-Quinoxaline-Type Bridged-Piperidine Compounds typically will have an ORL-1 GTP EC_{50} (nM) of about 5000 or less to stimulate ORL-1 receptor function. In one embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have an ORL-1 GTP EC_{50} (nM) of about 1000 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have an ORL-1 GTP EC_{50} (nM) of about 100 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have an ORL-1 GTP EC_{50} (nM) of about 80 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have an ORL-1 GTP EC_{50} (nM) of about 50 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have an ORL-1 GTP EC_{50} (nM) of about 35 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have an ORL-1 GTP EC_{50} (nM) of about 15 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have an ORL-1 GTP EC_{50} (nM) of about 10 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have an ORL-1 GTP EC_{50} (nM) of about 4 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have an ORL-

1 GTP EC_{50} (nM) of about 1 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have an ORL-1 GTP EC_{50} (nM) of about 0.4 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have an ORL-1 GTP EC_{50} (nM) of about 0.1 or less.

ORL-1 GTP Emax (%) is the maximal effect elicited by a compound relative to the effect elicited by nociceptin, a standard ORL-1 agonist. Typically, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have an ORL-1 GTP Emax (%) of greater than about 50%. In one embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compound Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have an ORL-1 GTP Emax (%) of greater than about 75%. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have an ORL-1 GTP Emax (%) of greater than about 85%. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have an ORL-1 GTP Emax (%) of greater than about 95%. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have an ORL-1 GTP Emax (%) of about 100% or greater. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have an ORL-1 GTP Emax (%) of about 110% or greater. Typically, a Substituted-Quinoxaline-Type Bridged-Piperidine Compound of the invention acting as a partial agonist will have an ORL-1 GTP Emax (%) of less than about 10%. In one embodiment, partial agonist Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have an ORL-1 GTP Emax (%) of less than about 20%. In another embodiment, partial agonist Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have an ORL-1 GTP Emax (%) of less than about 30%. In another embodiment, partial agonist Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have an ORL-1 GTP Emax (%) of less than about 40%. In another embodiment, partial agonist Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have an ORL-1 GTP Emax (%) of less than about 50%.

5.12 Example 12: *In vitro* Mu-opioid Receptor Binding Assays

μ-Opioid Receptor Binding Assay Procedures: Radioligand dose-displacement binding assays for μ-opioid receptors used 0.2nM[^{3}H]-diprenorphine (NEN, Boston, Mass.), with 5-20mg membrane protein/well in a final volume of 500μL binding buffer (10mM $MgCl_2$, 1mM EDTA, 5% DMSO, 50mM HEPES, pH 7.4). Reactions were carried out in the absence or presence of increasing concentrations of unlabeled naloxone. All reactions were conducted in 96-deep well polypropylene plates for 1-2 hr at about 25°C. Binding reactions were terminated by rapid filtration onto 96-well Unifilter GF/C filter plates (Packard, Meriden, Conn.) presoaked in 0.5% polyethylenimine using a 96-well tissue harvester (Brandel, Gaithersburg, Md.) followed by performing three filtration washes with 500μL of ice-cold binding buffer. Filter plates were

subsequently dried at 50°C for 2-3 hours. BetaScint scintillation cocktail (Wallac, Turku, Finland) was added (50μL/well), and plates were counted using a Packard Top-Count for 1 min/well. The data were analyzed using the one-site competition curve fitting functions in GraphPad PRISM v. 3.0 (San Diego, Calif.), or an in-house function for one-site competition curve-fitting.

μ-Opioid Receptor Binding Data: Typically, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a K_i (nM) of about 3000 or less for binding to μ-opioid receptors. In one embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a K_i (nM) of about 1000 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a K_i (nM) of about 650 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a K_i (nM) of about 525 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a K_i (nM) of about 250 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a K_i (nM) of about 100 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a K_i (nM) of about 10 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a K_i (nM) of about 1 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a K_i (nM) of about 0.1 or less.

5.13 Example 13: *In vitro* Mu-Opioid Receptor Functional Assays

μ-Opioid Receptor Functional Assay Procedures: [^{35}S]GTPγS functional assays were conducted using freshly thawed μ-receptor membranes. Assay reactions were prepared by sequentially adding the following reagents to binding buffer (100mM NaCl, 10mM $MgCl_2$, 20mM HEPES, pH 7.4) on ice (final concentrations indicated): membrane protein (0.026mg/mL), saponin (10mg/mL), GDP (3mM) and [^{35}S]GTPγS (0.20nM; NEN). The prepared membrane solution (190μL/well) was transferred to 96-shallow well polypropylene plates containing 10μL of 20x concentrated stock solutions of the agonist DAMGO ([D-Ala2, N-methyl-Phe4 Gly-ol5]-enkephalin) prepared in DMSO. Plates were incubated for 30min at about 25°C with shaking. Reactions were terminated by rapid filtration onto 96-well Unifilter GF/B filter plates (Packard, Meriden, Conn.) using a 96-well tissue harvester (Brandel, Gaithersburg, Md.) followed by three filtration washes with 200μL of ice-cold wash buffer (10mM NaH_2PO_4, 10mM Na_2HPO_4, pH 7.4). Filter plates were subsequently dried at 50°C for 2-3 hr. BetaScint scintillation cocktail (Wallac, Turku, Finland) was added (50μL/well) and plates were counted using a Packard Top-Count for 1 min/well. Data were analyzed using the sigmoidal dose-response curve fitting functions in

GraphPad PRISM v. 3.0, or an in-house function for non-linear, sigmoidal dose-response curve-fitting.

μ-Opioid Receptor Functional Data: μ GTP EC_{50} is the concentration of a compound providing 50% of the maximal response for the compound at a μ-opioid receptor. Substituted-Quinoxaline-Type Bridged-Piperidine Compounds typically will have a μ GTP EC_{50} (nM) of about 5000 or less to stimulate μ-opioid receptor function. In one embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a μ GTP EC_{50} (nM) of about 4100 or less. In one embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a μ GTP EC_{50} (nM) of about 3100 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a μ GTP EC_{50} (nM) of about 2000 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a μ GTP EC_{50} (nM) of about 1000 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a μ GTP EC_{50} (nM) of about 100 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a μ GTP EC_{50} (nM) of about 10 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a μ GTP EC_{50} (nM) of about 1 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a μ GTP EC_{50} (nM) of about 0.4 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a μ GTP EC_{50} (nM) of about 0.1 or less.

μ GTP Emax (%) is the maximal effect elicited by a compound relative to the effect elicited by DAMGO, a standard μ agonist. Typically, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a μ GTP Emax (%) of greater than about 10%. In one embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a μ GTP Emax (%) of greater than about 20%. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a μ GTP Emax (%) of greater than about 50%. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a μ GTP Emax (%) of greater than about 65%. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a μ GTP Emax (%) of greater than about 75%. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a μ GTP Emax (%) of greater than about 88%. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a μ GTP Emax (%) of about 100% or greater.

5.14 Example 14: *In vitro* Kappa-opioid Receptor Binding Assays

κ-Opioid Receptor Binding Assay Procedures: Membranes from recombinant HEK-293 cells expressing the human kappa opioid receptor (kappa) (cloned in house) were prepared by lysing cells in ice cold hypotonic buffer (2.5mM $MgCl_2$, 50mM HEPES, pH 7.4) (10mL/10 cm dish) followed by homogenization with a tissue grinder/Teflon pestle. Membranes were collected by centrifugation at 30,000 x g for 15min at 4°C and pellets resuspended in hypotonic buffer to a final concentration of 1-3mg/mL. Protein concentrations were determined using the BioRad protein assay reagent with bovine serum albumen as a standard. Aliquots of kappa receptor membranes were stored at -80 °C.

Radioligand dose displacement assays used 0.4-0.8nM [^{3}H]-U69,593 (NEN; 40 Ci/mmole) with 10-20μg membrane protein (recombinant kappa opioid receptor expressed in HEK 293 cells; in-house prep) in a final volume of 200μL binding buffer (5% DMSO, 50mM Trizma base, pH 7.4). Non-specific binding was determined in the presence of 10μM unlabeled naloxone or U69,593. All reactions were performed in 96-well polypropylene plates for 1 h at a temperature of about 25°C. Binding reactions were determined by rapid filtration onto 96-well Unifilter GF/C filter plates (Packard) presoaked in 0.5% polyethylenimine (Sigma). Harvesting was performed using a 96-well tissue harvester (Packard) followed by five filtration washes with 200μL ice-cold binding buffer. Filter plates were subsequently dried at 50°C for 1-2 hours. Fifty μL/well scintillation cocktail (MicroScint20, Packard) was added and plates were counted in a Packard Top-Count for 1 min/well.

κ-Opioid Receptor Binding Data: Typically, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 20,000 or less for κ receptors. In one embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 10,000 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 5000 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 1000 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 500 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 300 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 100 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 50 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 20 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 15 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 10 or less.

5.15 Example 15: *In vitro* Kappa-Opioid Receptor Functional Assays

κ-Opioid Receptor Functional Assay Procedures: Functional [^{35}S]GTPγS binding assays were conducted as follows. Kappa opioid receptor membrane solution was prepared by sequentially adding final concentrations of 0.026μg/μL kappa membrane protein (in-house), 10μg/mL saponin, 3μM GDP and 0.20nM [^{35}S]GTPγS to binding buffer (100mM NaCl, 10mM $MgCl_2$, 20mM HEPES, pH 7.4) on ice. The prepared membrane solution (190μL/well) was transferred to 96-shallow well polypropylene plates containing 10μL of 20x concentrated stock solutions of agonist prepared in DMSO. Plates were incubated for 30min at a temperature of about 25°C with shaking. Reactions were terminated by rapid filtration onto 96-well Unifilter GF/B filter plates (Packard) using a 96-well tissue harvester (Packard) and followed by three filtration washes with 200μL ice-cold binding buffer (10mM NaH_2PO_4, 10mM Na_2HPO_4, pH 7.4). Filter plates were subsequently dried at 50°C for 2-3 hours. Fifty μL/well scintillation cocktail (MicroScint20, Packard) was added and plates were counted in a Packard Top-Count for 1 min/well.

κ-Opioid Receptor Functional Data: κ GTP EC_{50} is the concentration of a compound providing 50% of the maximal response for the compound at a κ receptor. Substituted-Quinoxaline-Type Bridged-Piperidine Compounds typically will have a κ GTP EC_{50} (nM) of about 20,000 or less to stimulate κ opioid receptor function. In one embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 10,000 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 5000 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 2000 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 1500 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 800 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 500 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 300 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 100 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 50 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 25 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a κ GTP EC_{50} (nM) of about 10 or less.

κ GTP Emax (%) is the maximal effect elicited by a compound relative to the effect elicited by U69,593. Typically, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the

invention will have a κ GTP Emax (%) of greater than about 10%. In one embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a κ GTP Emax (%) of greater than about 15%. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a κ GTP Emax (%) of greater than about 30%. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a κ GTP Emax (%) of greater than about 40%. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a κ GTP Emax (%) of greater than about 45%. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a κ GTP Emax (%) of greater than about 75%. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a κ GTP Emax (%) of greater than about 90%. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a κ GTP Emax (%) of about 100% or greater.

5.16 Example 16: *In vitro* Delta-opioid Receptor Binding Assays

δ-Opioid Receptor Binding Assay Procedures: Radioligand dose-displacement assays used 0.2nM [^{3}H]-Naltrindole (NEN; 33.0 Ci/mmole) with 10-20μg membrane protein (recombinant delta opioid receptor expressend in CHO-K1 cells; Perkin Elmer) in a final volume of 500μL binding buffer (5mM $MgCl_2$, 5% DMSO, 50mM Trizma base, pH 7.4). Non-specific binding was determined in the presence of 25μM unlabeled naloxone. All reactions were performed in 96-deep well polypropylene plates for 1 h at a temperature of about 25°C. Binding reactions were determined by rapid filtration onto 96-well Unifilter GF/C filter plates (Packard) presoaked in 0.5% polyethylenimine (Sigma). Harvesting was performed using a 96-well tissue harvester (Packard) followed by five filtration washes with 500μL ice-cold binding buffer. Filter plates were subsequently dried at 50°C for 1-2 hours. Fifty μL/well scintillation cocktail (MicroScint20, Packard) was added and plates were counted in a Packard Top-Count for 1 min/well.

δ-Opioid Receptor Binding Data: Typically, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 20,000 or less for δ receptors. In one embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 10,000 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 7500 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 6500 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 5000 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 3000 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 2500 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-

Piperidine Compounds will have a Ki (nM) of about 1000 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 500 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 350 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 250 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 100 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a Ki (nM) of about 10 or less.

5.17 Example 17: *In vitro* Delta-Opioid Receptor Functional Assays

δ-Opioid Receptor Functional Assay Procedures: Functional [^{35}S]GTPγS binding assays were conducted as follows. Delta opioid receptor membrane solution was prepared by sequentially adding final concentrations of 0.026μg/μL delta membrane protein (Perkin Elmer), 10μg/mL saponin, 3μM GDP and 0.20nM [^{35}S]GTPγS to binding buffer (100mM NaCl, 10mM $MgCl_2$, 20mM HEPES, pH 7.4) on ice. The prepared membrane solution (190μL/well) was transferred to 96-shallow well polypropylene plates containing 10μL of 20x concentrated stock solutions of agonist prepared in DMSO. Plates were incubated for 30min at a temperature of about 25°C with shaking. Reactions were terminated by rapid filtration onto 96-well Unifilter GF/B filter plates (Packard) using a 96-well tissue harvester (Packard) and followed by three filtration washes with 200μL ice-cold binding buffer (10mM NaH_2PO_4, 10mM Na_2HPO_4, pH 7.4). Filter plates were subsequently dried at 50°C for 1-2 hours. Fifty μL/well scintillation cocktail (MicroScint20, Packard) was added and plates were counted in a Packard Top-count for 1 min/well.

δ-Opioid Receptor Functional Data: δ GTP EC_{50} is the concentration of a compound providing 50% of the maximal response for the compound at a δ receptor. Substituted-Quinoxaline-Type Bridged-Piperidine Compounds typically will have a δ GTP EC_{50} (nM) of about 20,000 or less to stimulate δ opioid receptor function. In one embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a δ GTP EC_{50} (nM) of about 10,000 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a δ GTP EC_{50} (nM) of about 100 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a δ GTP EC_{50} (nM) of about 1000 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a δ GTP EC_{50} (nM) of about 90 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a δ GTP EC_{50} (nM) of about 50 or less. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a δ GTP EC_{50} (nM) of about 25 or less. In another embodiment, the Substituted-

Quinoxaline-Type Bridged-Piperidine Compounds will have a δ GTP EC_{50} (nM) of about 10 or less.

δ GTP Emax (%) is the maximal effect elicited by a compound relative to the effect elicited by met-enkephalin. Typically, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds of the invention will have a δ GTP Emax (%) of greater than about 10%. In one embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a δ GTP Emax (%) of greater than about 30%. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a δ GTP Emax (%) of greater than about 50%. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a δ GTP Emax (%) of greater than about 75%. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a δ GTP Emax (%) of greater than about 90%. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a δ GTP Emax (%) of about 100% or greater. In another embodiment, the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds will have a δ GTP Emax (%) of about 110% or greater.

5.18 Example 18: Efficacy of Receptor Binding and Activity Response

The following Tables provide results on the efficacy of binding and activity response of several Substituted-Quinoxaline-Type Bridged-Piperidine Compounds to the ORL-1 receptor and, for certain Substituted-Quinoxaline-Type Bridged-Piperidine Compounds, the mu-opioid receptor, the kappa-opioid receptor, and/or the delta-opioid receptor.

In Table 1, binding efficacy to the ORL-1 receptor was determined by the procedure in Example 10. Binding efficacy to the mu-opioid receptor was determined by the procedure in Example 12. Binding efficacy to the kappa-opioid receptor was determined by the procedure in Example 14. Binding efficacy to the delta-opioid receptor was determined by the procedure in Example 16.

In Table 2, activity response to the ORL-1 receptor was determined by the procedure in Example 11. Activity response to the mu-opioid receptor was determined by the procedure in Example 13. Activity response to the kappa-opioid receptor was determined by the procedure in Example 15. Activity response to the delta-opioid receptor can be determined by the procedure in Example 17.

Table 1: Efficacy of Receptor Binding of Substituted-Quinoxaline-Type Bridged-Piperidine Compounds

Ref No.	K_i [Average ± Std Deviation] (nM)			
	ORL-1	Opioid Receptor		
		Mu	Kappa	Delta
356	43.1±3.4	1436±215	76±21	18180
358	9.0±1.1	1600±55	640±126	8900±2390
360	202.8±7.1	3825±576	2691±189	> 20,000
361	5.7±0.4	4450±1224	6143±1617	> 20,000
362	2.4±0.2	1631±77	2280±213	4763±509
369	178±17	4032±1010	5345±1725	> 20,000
405	1.1±0.1	61.6±8.7	75.4±7.8	691±57

Table 2: Activity Response of Substituted-Quinoxaline-Type Bridged-Piperidine Compounds

Ref No.	GTPγS (EC_{50}: nM, Emax: %) [mean ± SEM]					
	ORL-1		Opioid Receptor			
			Mu		Kappa	
	EC_{50}	E_{max}	EC_{50}	E_{max}	EC_{50}	E_{max}
356	686±41	93.3±8			> 20,000	3.3±1.2
358	62.6±14.1	101.3±5.7	17,800± 14,600	9.7±0.9	1960±806	11.7±2.3
360	1667.1±18.4	57.3±4.1				
361	57.2±3.1	58.7±2.4	> 20,000	0	> 20,000	9.7±5.6
362	4.03±0.86	47.8±1.3	> 20,000	0	> 20,000	3.0±0.6
369	545±85	37.7±0.7				
405	0.55±0.1	47.5±3.5	> 20,000	0	> 20,000	0

5.19 Example 19: *In Vivo* Assays for Prevention or Treatment of Pain

Test Animals: Each experiment used rats weighing between 200-260g at the start of the experiment. The rats were group-housed and had free access to food and water at all times, except prior to oral administration of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound when food was removed for 16 hours before dosing. A control group acted as a comparison to rats treated with a Substituted-Quinoxaline-Type Bridged-Piperidine Compound. The control group was administered the carrier for the Substituted-Quinoxaline-Type Bridged-Piperidine Compound. The volume of carrier administered to the control group was the same as the volume of carrier and Substituted-Quinoxaline-Type Bridged-Piperidine Compound administered to the test group.

Acute Pain: To assess the actions of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound for the treatment or prevention of acute pain, the rat tail flick test can be used. Rats are gently restrained by hand and the tail exposed to a focused beam of radiant heat at a point 5 cm from the tip using a tail flick unit (Model 7360, commercially available from Ugo Basile of Italy). Tail flick latencies are defined as the interval between the onset of the thermal stimulus and the flick of the tail. Animals not responding within 20 seconds are removed from the tail flick unit and assigned a withdrawal latency of 20 seconds. Tail flick latencies are measured immediately before (pre-treatment) and 1, 3, and 5 hours following administration of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound. Data are expressed as tail flick latency(s) and the percentage of the maximal possible effect (% MPE), *i.e.*, 20 seconds, is calculated as follows:

$$\%\ \text{MPE} = \frac{[\ (\text{post administration latency}) - (\text{pre-administration latency})\ ]}{(20\ \text{s pre-administration latency})} \times 100$$

The rat tail flick test is described in F.E. D'Amour *et al.*, "A Method for Determining Loss of Pain Sensation," *J. Pharmacol. Exp. Ther.* 72:74-79 (1941).

Inflammatory Pain: To assess the actions of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound for the treatment or prevention of inflammatory pain, the Freund's complete adjuvant ("FCA") model of inflammatory pain was used. FCA-induced inflammation of the rat hind paw is associated with the development of persistent inflammatory mechanical and thermal hyperalgesia and provides reliable prediction of the anti-hyperalgesic action of clinically useful analgesic drugs (L. Bartho *et al.*, "Involvement of Substituted-Quinoxaline-Type Bridged-Piperidine Compound Inflammation," *Naunyn-Schmiedeberg's Archives of Pharmacol.* 342:666-670 (1990)). The left hind paw of each animal was administered a 50 µL intraplantar injection of 50% FCA. 24 hour post injection, the animal was assessed for response to noxious mechanical stimuli by determining the PWT, or to noxious thermal stimuli by determining the PWL, as

described below. Rats were then administered a single injection of 0.1, 0.3, 1, 3, 10 or 30mg/kg of either a Substituted-Quinoxaline-Type Bridged-Piperidine Compound; 30mg/kg of a control selected from Celebrex, indomethacin or naproxen; or carrier. Responses to noxious mechanical stimuli were then determined 1, 3, 5 and 24 hours post administration. Percentage reversal of hyperalgesia for each animal was defined as:

$$\% \text{ Reversal} = \frac{[\text{(post administration PWT/PWL)} - \text{(pre-administration PWT/PWL)}]}{[\text{(baseline PWT)} - \text{(pre-administration PWT)}]} \times 100$$

Assessments of the actions of the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds that were tested revealed these compounds were efficacious, *e.g.*, Substituted-Quinoxaline-Type Bridged-Piperidine Compounds significantly reduced FCA-induced thermal hyperalgesia, with ED_{50} values of from about 0.1 mg/kg to about 20 mg/kg and maximum % reversal values of from about 20% to about 100%. For example, for the Substituted Quinoxaline-Type Bridged-Piperidine Compound **362**, the ED_{50} value for reversal of thermal hyperalgesia was 0.8mg/kg at 1 hour after administration, 1.5mg/kg at 3 hours after administration, and 3.0mg/kg at 5 hours after administration of Substituted Quinoxaline-Type Bridged-Piperidine Compound **362**. Additionally, the % reversal of thermal hyperalgesia after administration of a 3mg/kg dose was 86% at 1 hour after administration, 51% at 3 hours after administration, and 27% at 5 hours after administration of Substituted Quinoxaline-Type Bridged-Piperidine Compound **362**. And, for Substituted Quinoxaline-Type Bridged-Piperidine Compound **361**, upon administration of a 5mg/kg dose, the % reversal of thermal hyperalgesia was 36% reversal at 1 hour after administration, 90% reversal at 3 hours after administration, and 70% reversal at 5 hours after administration of Substituted Quinoxaline-Type Bridged-Piperidine Compound **361**. And, for Substituted Quinoxaline-Type Bridged-Piperidine Compound **358**, upon administration of 5mg/kg dose, the % reversal of thermal hyperalgesia was 34% reversal at 1 hour after administration, 46% reversal at 3 hours after administration, and 79% reversal at 5 hours after administration of Substituted Quinoxaline-Type Bridged-Piperidine Compound **358**.

Substituted Quinoxaline-Type Bridged-Piperidine Compounds **358**, **361**, and **362** also have surprisingly and desirably reduced abnormal behavioral side effects, such as reduced sedation, hyperactivity and/or hypoactivity. Additionally and surprisingly, Substituted Quinoxaline-Type Bridged-Piperidine Compound **362** has reduced cardiovascular side effects. These side effects were determined using known methods: an *in vitro* hERG (human ether a-go-go gene) assay as disclosed in Z. Zhou et al., "Properties of HERG Channels Stably Expressed in HEK 293 Cells Studied at Physiological Temperature," *Biophysical J.* 74:230-241 (1998); and APD (action

potential duration) in guinea pig purkinje fibers as disclosed in J.A. Hey, "The Guinea Pig Model for Assessing Cardiotoxic Proclivities of Second Generation Antihistamines," *Arzneimittelforschung* 46(8):834-837 (1996).

Neuropathic Pain: To assess the actions of a Substituted-Quinoxaline-Type Bridged-Piperidine Compound for the treatment or prevention of neuropathic pain, either the Seltzer model or the Chung model can be used.

In the Seltzer model, the partial sciatic nerve ligation model of neuropathic pain was used to produce neuropathic hyperalgesia in rats (Z. Seltzer *et al.*, "A Novel Behavioral Model of Neuropathic Pain Disorders Produced in Rats by Partial Sciatic Nerve Injury," *Pain* 43:205-218 (1990)). Partial ligation of the left sciatic nerve was performed under isoflurane/O_2 inhalation anesthesia. Following induction of anesthesia, the left thigh of the rat was shaved and the sciatic nerve exposed at high thigh level through a small incision and was carefully cleared of surrounding connective tissues at a site near the trocanther just distal to the point at which the posterior biceps semitendinosus nerve branches off of the common sciatic nerve. A 7-0 silk suture was inserted into the nerve with a 3/8 curved, reversed-cutting mini-needle and tightly ligated so that the dorsal 1/3 to ½ of the nerve thickness was held within the ligature. The wound was closed with a single muscle suture (4-0 nylon (Vicryl)) and vetbond tissue glue. Following surgery, the wound area was dusted with antibiotic powder. Sham-treated rats underwent an identical surgical procedure except that the sciatic nerve was not manipulated. Following surgery, animals were weighed and placed on a warm pad until they recovered from anesthesia. Animals were then returned to their home cages until behavioral testing began. The animals were assessed for response to noxious mechanical stimuli by determining PWT, as described below, prior to surgery (baseline), then immediately prior to and 1, 3, and 5 hours after drug administration for rear paw of the animal. Percentage reversal of neuropathic hyperalgesia was defined as:

$$\% \text{ Reversal} = \frac{[\text{(post administration PWT)} - \text{(pre-administration PWT)}]}{[\text{(baseline PWT)} - \text{(pre-administration PWT)}]} \times 100$$

Assessments of the actions of the Substituted-Quinoxaline-Type Bridged-Piperidine Compounds that were tested revealed that these compounds were efficacious, *e.g.* Substituted-Quinoxaline-Type Bridged-Piperidine Compounds significantly reduced nerve injury-induced mechanical hyperalgesia, with ED_{50} values from about 0.3 mg/kg to about 20 mg/kg and maximum % reversal values of from about 20% to about 70%. For example, for the Substituted-Quinoxaline-Type Bridged-Piperidine **362**, the % reversal of mechanical hyperalgesia after administration of 3 mg/kg was 60% at 1 and 3 hours after administration, 50% at 5 hours, and 40% at 7 hours. And,

for Substituted-Quinoxaline-Type Bridged-Piperidine Compound **405**, upon administration of a 3 mg/kg dose, the % reversal of mechanical hyperalgesia was 70% at 1, 3 and 5 hours after administration of the Substituted-Quinoxaline-Type Bridged-Piperidine Compound **405**.

The Chung model may also be used to assess neuropathic hyperalgesia. In the Chung model, the spinal nerve ligation model of neuropathic pain is used to produce mechanical hyperalgesia, thermal hyperalgesia and tactile allodynia in rats. Surgery is performed under isoflurane/O_2 inhalation anesthesia. Following induction of anesthesia, a 3 cm incision is made and the left paraspinal muscles are separated from the spinous process at the L_4-S_2 levels. The L_6 transverse process is carefully removed with a pair of small rongeurs to identify visually the L_4-L_6 spinal nerves. The left L_5 (or L_5 and L_6) spinal nerve(s) is isolated and tightly ligated with silk thread. A complete hemostasis is confirmed and the wound is sutured using non-absorbable sutures, such as nylon sutures or stainless steel staples. Sham-treated rats undergo an identical surgical procedure except that the spinal nerve(s) is not manipulated. Following surgery animals are weighed, administered a subcutaneous (s.c.) injection of saline or ringers lactate, the wound area is dusted with antibiotic powder and they are kept on a warm pad until they recover from the anesthesia. Animals are then returned to their home cages until behavioral testing begins. The animals are assessed for response to noxious mechanical stimuli by determining PWT, as described below, prior to surgery (baseline), then immediately prior to and 1, 3, and 5 hours after being administered a Substituted-Quinoxaline-Type Bridged-Piperidine Compound for the left rear paw of the animal. The animal can also be assessed for response to noxious thermal stimuli or for tactile allodynia, as described below. The Chung model for neuropathic pain is described in S.H. Kim, "An Experimental Model for Peripheral Neuropathy Produced by Segmental Spinal Nerve Ligation in the Rat," *Pain* 50(3):355-363 (1992).

Response to Mechanical Stimuli as an Assessment of Mechanical Hyperalgesia: The paw pressure assay was used to assess mechanical hyperalgesia. For this assay, hind paw withdrawal thresholds (PWT) to a noxious mechanical stimulus were determined using an analgesymeter (Model 7200, commercially available from Ugo Basile of Italy) as described in C. Stein, "Unilateral Inflammation of the Hindpaw in Rats as a Model of Prolonged Noxious Stimulation: Alterations in Behavior and Nociceptive Thresholds," *Pharmacol. Biochem. and Behavior* 31:451-455 (1988). The maximum weight that could be applied to the hind paw was set at 250 g and the end point is taken was complete withdrawal of the paw. PWT was determined once for each rat at each time point and either only the affected (ipsilateral) paw was tested, or both the ipsilateral and contralateral (non-injured) paw were tested.

Response to Thermal Stimuli as an Assessment of Thermal Hyperalgesia: The plantar test can be used to assess thermal hyperalgesia. For this test, hind paw withdrawal latencies (PWL) to a noxious thermal stimulus were determined using a plantar test apparatus (commercially

available from Ugo Basile of Italy) following the technique described by K. Hargreaves *et al.*, "A New and Sensitive Method for Measuring Thermal Nociception in Cutaneous Hyperalgesia," *Pain* 32(1):77-88 (1988). The maximum exposure time was set at 32 seconds to avoid tissue damage and any directed paw withdrawal from the heat source was taken as the end point. Three latencies were determined at each time point and averaged. Either only the affected (ipsilateral) paw was tested, or both the ipsilateral and contralateral (non-injured) paw were tested.

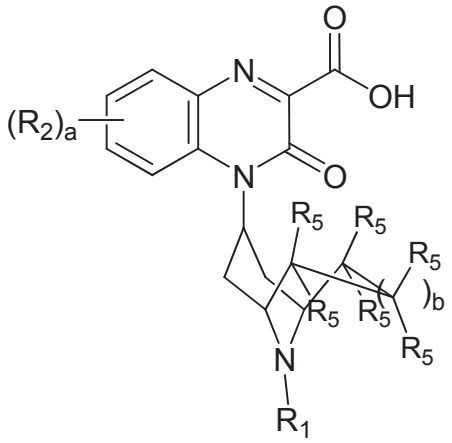
Assessment of Tactile Allodynia: To assess tactile allodynia, rats are placed in clear, Plexiglas compartments with a wire mesh floor and allowed to habituate for a period of at least 15minutes. After habituation, a series of von Frey monofilaments are presented to the plantar surface of the left (operated) foot of each rat. The series of von Frey monofilaments consists of six monofilaments of increasing diameter, with the smallest diameter fiber presented first. Five trials are conducted with each filament with each trial separated by approximately 2 minutes. Each presentation lasts for a period of 4-8 seconds or until a nociceptive withdrawal behavior is observed. Flinching, paw withdrawal or licking of the paw are considered nociceptive behavioral responses.

The invention is not to be limited in scope by the specific embodiments disclosed in the examples that are intended as illustrations of a few aspects of the invention and any embodiments that are functionally equivalent are within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art and are intended to fall within the scope of the appended claims.

A number of references have been cited, the entire disclosures of which are incorporated herein by reference for all purposes.

Claims

1. A compound of Formula (I'):



(I')

or a pharmaceutically acceptable derivative thereof wherein:

each R_2 is independently selected from -halo;

a is an integer selected from 0, 1 or 2;

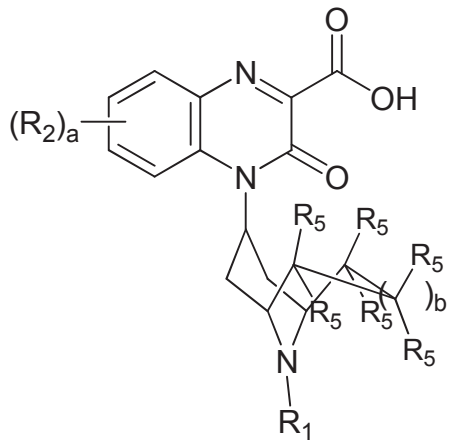
b is an integer selected from 0 or 1;

each R_5 is independently selected from -H, -OH, -(C_1-C_3)alkyl, -C(halo)$_3$, or -halo;

R_1 is -(C_9-C_{14})cycloalkyl or -(C_9-C_{14})bicycloalkyl, each of which is substituted with 1, 2 or 3 independently selected R_3 groups;

each R_3 is independently selected from -(C_1-C_4)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, or -(C_3-C_6)cycloalkyl, and wherein the pharmaceutically acceptable derivative is selected from the group consisting of pharmaceutically acceptable salt, solvate, radiolabeled, stereoisomer, enantiomer, diastereomer, racemic mixture, and tautomer.

2. A compound of Formula (I):



(I)

or a pharmaceutically acceptable derivative thereof wherein:

each R_2 is independently selected from -halo;

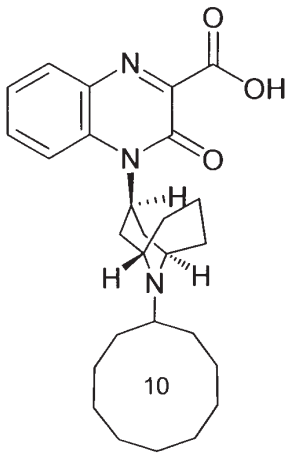
a is an integer selected from 0, 1 or 2;

b is an integer selected from 0 or 1;

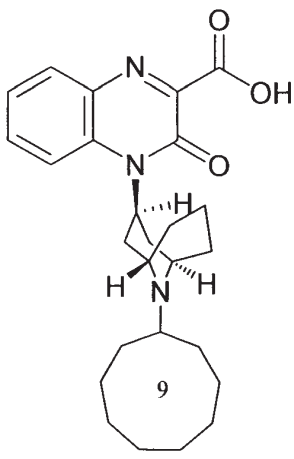
each R_5 is independently selected from -H, -OH, -(C_1-C_3)alkyl, -C(halo)$_3$, or -halo;

R_1 is -(C_9-C_{14})cycloalkyl or -(C_9-C_{14})bicycloalkyl; and

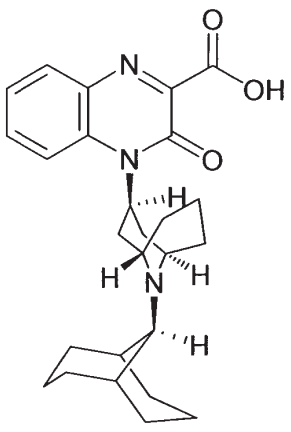
each halo is independently selected from -F, -Cl, -Br, or -I, and wherein the pharmaceutically acceptable derivative is selected from the group consisting of pharmaceutically acceptable salt, solvate, radiolabeled, stereoisomer, enantiomer, diastereomer, racemic mixture, and tautomer, with the proviso that the compound is not



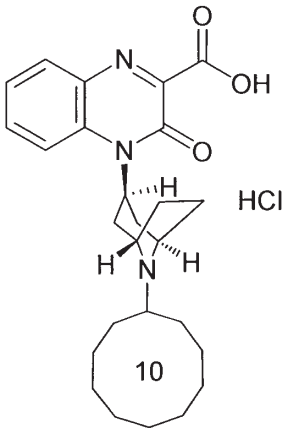
,

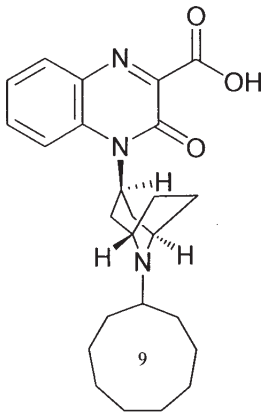


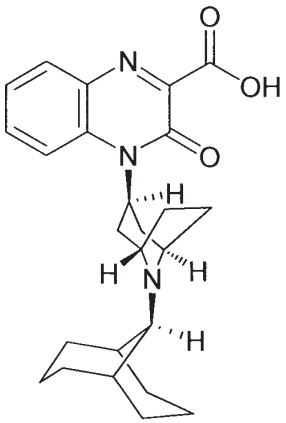
,

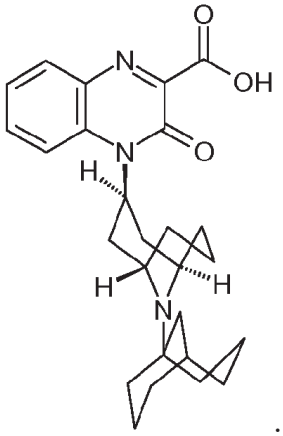


,



,


,


, or


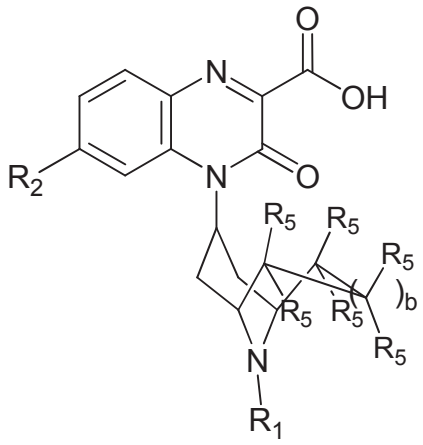
.

3. The compound of claims 1 or 2, wherein each R_5 is independently selected from -H, -$(C_1$-$C_3)$alkyl, -C(halo)$_3$, or -halo.

4. The compound of any one of claims 1 to 3, wherein each R_5 is independently selected from -H, -CH_3, -CF_3, or –F, and preferably each R_5 is -H.

5. The compound of any one of claims 1 to 4, wherein a is an integer selected from 0 or 1 and preferably is 0.

6. The compound of any one of claims 1 to 5, wherein the compound is a compound of formula (II):



(II)

or a pharmaceutically acceptable derivative thereof, wherein the pharmaceutically acceptable derivative is selected from the group consisting of pharmaceutically acceptable salt, solvate, radiolabeled, stereoisomer, enantiomer, diastereomer, racemic mixture, and tautomer.

7. The compound of any one of claims 1 to 6, wherein R_2 is -F.

8. The compound of any one of claims 1 to 7, wherein the 3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid portion of the compound is in the *endo-* or *exo-* conformation with respect to the bridge of the bridged piperidine, and preferably is in the *endo-* conformation.

9. The compound of any one of claims 1 to 8, wherein R_1 is -(C_9-C_{12})cycloalkyl or -(C_9-C_{12})bicycloalkyl, and wherein preferably

(i) R_1 is -(C_9-C_{12})bicycloalkyl, or

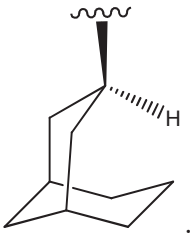
(ii) R_1 is -indanyl, -1,2,3,4-tetrahydronaphthalenyl, -5,6,7,8-tetrahydronaphthalenyl, -perhydronaphthalenyl, bicyclo[3.3.1]nonyl, bicyclo[4.2.1]nonyl, bicyclo[3.3.2]decyl, bicyclo[4.2.2]decyl, bicyclo[4.3.1]decyl, bicyclo[3.3.3]undecyl, bicyclo[4.3.2]undecyl, or bicyclo[4.3.3]dodecyl, or

(iii) R_1 is cycloundecyl.

10. The compound of any one of claims 1 to 9, wherein R_1 is bicyclo[3.3.1]nonyl and preferably R_1 is 2-bicyclo[3.3.1]nonyl, or 3-bicyclo[3.3.1]nonyl.

11. The compound of any one of claims 1 to 10, wherein R_1 is in the *endo*- or *exo*-conformation with respect to the bridge of the bridged piperidine, and preferably is in the *exo*-conformation.

12. The compound of any one of claims 2 to 11, wherein R_1 is:



.

13. The compound of any one of claims 1, 3-11, wherein in a compound of formula (I') there are 1, 2 or 3 R_3 groups and each R_3 group is independently selected from

(i) -(C_1-C_4)alkyl, -(C_2-C_6)alkenyl, and -(C_2-C_6)alkynyl; or

(ii) -(C_1-C_4)alkyl and -(C_3-C_6)cycloalkyl.

14. The compound of any one of claims 1, 3-11 or 13, wherein in a compound of formula (I') each R_3 group is methyl.

15. The compound of any one of claims 1, 3-11 or 13-14, wherein in a compound of formula (I') one R_3 group is present.

16. The compound of any one of claims 1, 3-11, 13 or 15, wherein in a compound of formula (I') there is one R_3 group which is

(i) -(C_1-C_4)alkyl, -(C_2-C_6)alkenyl, or -(C_2-C_6)alkynyl; or

(ii) -(C_1-C_4)alkyl or -(C_3-C_6)cycloalkyl.

17. The compound of any one of claims 1, 3-11, 13 or 15-16, wherein in a compound of formula (I') there is one R_3 group which is

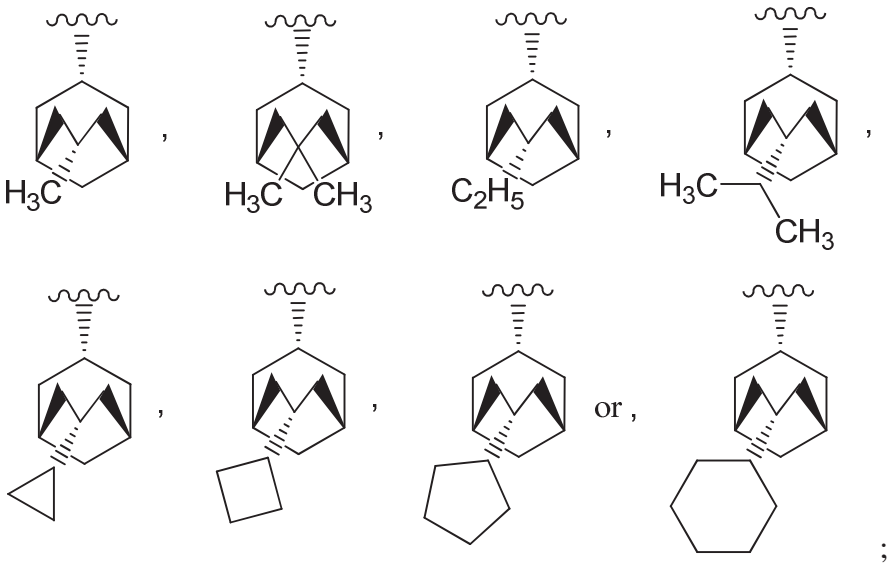
(i) -methyl, -ethyl, -n-propyl, -*iso*-propyl, -n-butyl, -*sec*-butyl, -*iso*-butyl, or -*tert*-butyl, or

(ii) -methyl, -ethyl, -*iso*-propyl, -*iso*-butyl, or -*tert*-butyl;

and preferably wherein R_3 is ethyl or methyl.

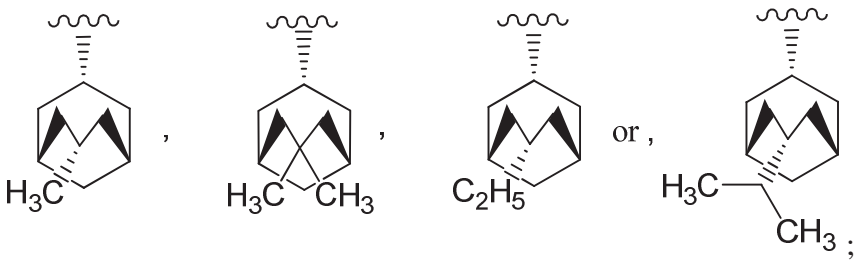
18. The compound of any one of claims 1 to 17, wherein in a compound of formula (I') the carbon atom of the R_1 group which is attached to the nitrogen atom of the bridged piperidine is unsubstituted by a R_3 group.

19. The compound of any one of claims 1, 3-11, 13-16, 17 options (i) and (ii) as well as R_3 being methyl, or 18, wherein in a compound of formula (I') R_1 and R_3 together are:



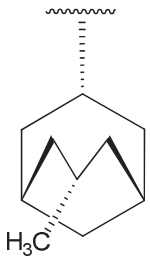
;

more preferably are:



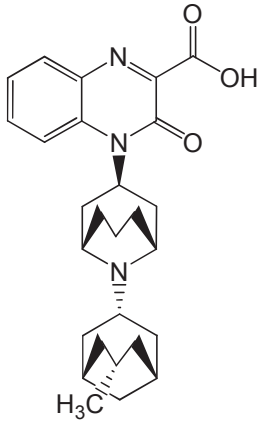
;

and most preferably are:



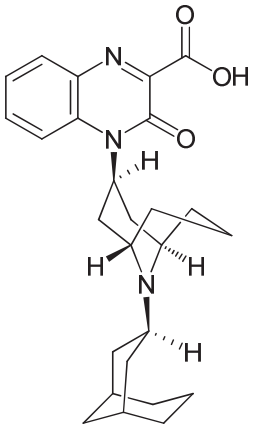
.

20. The compound of claim 1 having the formula:

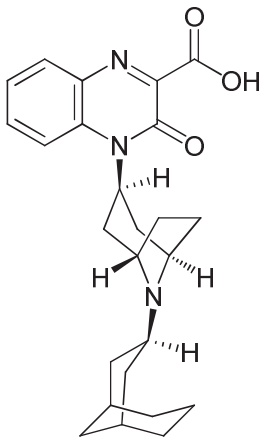


or a pharmaceutically acceptable derivative thereof, wherein the pharmaceutically acceptable derivative is selected from the group consisting of pharmaceutically acceptable salt, solvate, radiolabeled, stereoisomer, enantiomer, diastereomer, racemic mixture, and tautomer.

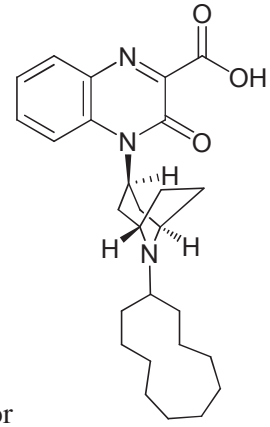
21. The compound of claim 2 having the formula:



,



, or



or a pharmaceutically acceptable derivative thereof, wherein the pharmaceutically acceptable derivative is selected from the group consisting of pharmaceutically acceptable salt, solvate, radiolabeled, stereoisomer, enantiomer, diastereomer, racemic mixture, and tautomer.

22. The compound of any one of claims 1 to 21, wherein the pharmaceutically acceptable derivative is a pharmaceutically acceptable salt, and preferably is a *p*-toluenesulfonic acid salt, a sulfate salt or a phosphoric acid salt and preferably is a *p*-toluenesulfonic acid salt.

23. A composition comprising an effective amount of the compound or a pharmaceutically acceptable derivative of the compound of any one of claims 1 to 22 and a pharmaceutically acceptable carrier or excipient.

24. An *in vitro* method for modulating ORL-1 receptor function in a cell, comprising contacting a cell capable of expressing the ORL-1 receptor with an effective amount of the compound or a pharmaceutically acceptable derivative of the compound of any one of claims 1 to 22, wherein the pharmaceutically acceptable derivative is selected from the group consisting of pharmaceutically acceptable salt, solvate, radiolabeled, stereoisomer, enantiomer, diastereomer, racemic mixture, and tautomer.

25. The *in vitro* method of claim 24, wherein the compound or the pharmaceutically acceptable derivative of the compound acts as an agonist at the ORL-1 receptor, as a partial agonist at the ORL-1 receptor, or as an antagonist at the ORL-1 receptor, wherein the pharmaceutically acceptable derivative is selected from the group consisting of pharmaceutically acceptable salt, solvate, radiolabeled, stereoisomer, enantiomer, diastereomer, racemic mixture, and tautomer.

26. A kit comprising a container containing an effective amount of the compound or a pharmaceutically acceptable derivative of the compound of any one of claims 1 to 22.

27. A method for preparing a composition, comprising the step of admixing a compound or a pharmaceutically acceptable derivative of the compound of any one of claims 1 to 22 and a pharmaceutically acceptable carrier or excipient.

28. Use of a compound of any one of claims 1 to 22 for the manufacture of a medicament useful for treating pain, a memory disorder, obesity, constipation, depression, dementia, Parkinsonism, anxiety, cough, diarrhea, high blood pressure, epilepsy, anorexia/cachexia, urinary incontinence, or drug abuse.